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Preface

On February 1, 2012, they came, and they came, and they came until it was standing room only. The word had gone out to providers at the Cincinnati Veterans Administration Medical Center that there was a meeting for everyone involved in the care of Veterans with Chronic Obstructive Pulmonary Disease (COPD). We had just been awarded a grant from the Office of Specialty Care entitled, “Patient-Centered Model for the Management of Chronic Obstructive Pulmonary Disease.” The goals for that proposal were to enhance the recognition and diagnosis of COPD and implement a Patient-Centered Model for the Management of COPD. We invited providers who we knew were interested in COPD to an inaugural planning and organizational meeting and asked them to spread the word and encourage others to attend – and they did. We planned to meet in a conference room with a capacity of 10–15 people but over thirty people attended that first meeting and we had to move to a larger room. Participants included respiratory therapists, primary care providers, pharmacists, tele-health providers, nurse practitioners, researchers, hospitalists, patient-aligned care team (PACT) members, psychologists, smoking cessation counselors, and pulmonologists.

In subsequent meetings, we were joined by University of Cincinnati researchers and Jack Kues, the Dean for Continuous Professional Development.

For the next three years, we met nearly every other Wednesday morning to review what and how care was being provided to Veterans with COPD; always asking what tools, new initiatives, or process changes were needed to improve that care. We traced the course of a Veteran with unrecognized, undiagnosed airflow limitation to initial COPD diagnosis including physiologic, radiographic, and laboratory testing. We identified the most appropriate next steps for starting treatment and management of outpatient and inpatient exacerbations. We recognized that optimal management of these patients would require transitions of care between primary care and subspecialists in both outpatient and inpatient settings. Best care also included the identification of pulmonary and nonpulmonary COPD manifestations and complications that in some cases would lead to palliative and end of life care. At each step, we asked how this care could be more patient-centric. Along that journey, Folarin Sogbetun developed a Veteran-specific COPD screening questionnaire that was tested, validated, and compared with other COPD screening surveys; Bill Eschenbacher created a telespirometry program with teaching modules, quality assurance reviews, and interpretation algorithms whose success triggered funding for the purchase of spirometers for every Community Based Outpatient Clinic (CBOC) nationally; we participated in a design course at the University of Cincinnati College of Design, Architecture, Art, and Planning during which students created projects to enhance patients’ management of COPD including the visual pill box designed by Siyuan Fan and presented in Figure 8.3.

During this process, we realized that providers did not have an up-to-date, comprehensive, easily read, “how to” manual for the management of COPD despite all
the advances in COPD care that have occurred over the past 5 years. Consensus documents such as the VA-DOD Guidelines were abbreviated summaries that were rarely used. From those discussions, the concept for this volume, a COPD Primer, developed. The goal was to develop a practical book that concisely presented COPD to providers with sufficient background and explanation of the physiologic and scientific rationale for various management strategies without becoming an esoteric academic work. We hope that this COPD Primer has achieved that goal and will be a useful, practical text for practitioners and medical trainees alike.

The COPD Primer begins with an examination of what COPD is; it is really a syndrome, a constellation of historical features and clinical, physiologic, and radiographic findings. However, those elements come together in many different ways to create multiple different COPD phenotypes that are only now being recognized and used to define specific management strategies. COPD research has progressed beyond the simple classification of “blue bloaters” and “pink puffers.” Next, the epidemiology and economic consequences of COPD are reviewed. Bill Eschenbacher presents an approach to the patient with respiratory symptoms with detailed discussions of pulmonary function testing and how airflow limitation/obstruction is identified by spirometry and the use of lung imaging to identify individuals with COPD. Michael Borchers and Gregory Motz summarize current evidence implicating genetics, proteolytic imbalance, oxidative stress, inflammation, occupational and environmental exposures, and innate and adaptive immune function in the pathogenesis of COPD and the implication of these findings to future treatments. The single most important intervention in the prevention and treatment of COPD is smoking cessation. Shari Altum, Katherine Butler, and Rachel Juran present a practical approach to smoking cessation utilizing motivational interviewing in combination with pharmacologic interventions. Then, they expand upon these concepts to provide practitioners with convenient, realistic suggestions to encourage patient self-management in all aspects of COPD care and overall health. Ahsan Zafar reviews the natural history, recently described COPD phenotypes, and gender differences that clearly illustrate the broad spectrum of disease that comprises the term, COPD. The cover illustration highlights Dr. Zafar’s creative and artistic talents. The extensive nonpulmonary aspects of COPD are reviewed by Ralph Panos in an examination of COPD’s multi-organ manifestations. Next, the effect of COPD on sleep and the overlap syndrome, the concurrence of COPD and obstructive sleep apnea, and its consequences are presented. Jean Elwing examines the effect of COPD on the pulmonary vasculature with a detailed discussion of the evaluation and management of pulmonary hypertension associated with COPD. COPD’s effects on psychosocial functioning and familial interactions are presented by Mary Panos and Ralph Panos.

The focus of the Primer then shifts from manifestations to treatment with a discussion of stable COPD management. With the current plethora of devices for delivering respiratory medications, it is difficult for both patients and providers to sustain knowledge of their proper use. Aaron Mulhall presents a practical guide to correct
inhaler use that reviews all the current devices. Folarin Sogbetun then reviews the management of outpatient COPD exacerbations and Nishant Gupta discusses the approach to the patient hospitalized with COPD. Because patients with COPD often see multiple subspecialty physicians in addition to their primary care providers, interdisciplinary communication and coordination of care is essential for their management; Sara Krzywkowski-Mohn reviews the interactions between primary and specialty care for the patient with COPD with suggestions for improved communication and care coordination. Finally, advance care planning including palliative care and hospice is reviewed with a discussion of how end stage COPD affects not only the patient but also their family and social network.

This COPD Primer incorporates the knowledge that we have learned over the past several years during the development and implementation of a patient-centered model for the management of COPD. It was written with an explicit goal of assisting both the practicing provider and medical trainee in the care of patients with COPD.

We thank Magdalena Wierzchowiecka, PhD, Managing Editor, Medicine, at De Gruyter Open, Ltd. for her assistance in editing and producing this work. We are grateful for all of the collaborating authors; their energy, work, and willingness to meet deadlines and quick responses to revisions and suggestions made this COPD Primer possible. We thank all the COPD working group members who participated in three years of Wednesday morning discussions that covered the spectrum of health care from the specifics of COPD to evolving national healthcare reform. The ultimate goal of this program and this book is the improvement of care for individuals with COPD and we thank all of our patients who motivate us to improve and continually strive to provide the best possible care.

We are very appreciative and thankful for the patience and encouragement of our wives, Jean and Judy, for tolerating all these months of writing, revising, and editing. Without your forbearance, this COPD Primer would never have made it to print.

Ralph J. Panos
William L. Eschenbacher

May 2, 2015
1 Introduction and Definition of Chronic Obstructive Pulmonary Disease COPD

Key Points
1. Chronic obstructive pulmonary disease (COPD) is a syndrome, a constellation of historical findings, clinical signs and symptoms, physiologic derangements, and radiologic abnormalities.
2. There is not a single test that can establish a diagnosis of COPD or exclude other similar processes.
3. Recent findings suggest multiple different COPD phenotypes which may have different clinical courses and responses to treatment.
4. COPD is usually characterized by airflow obstruction that does not fully normalize (return to predicted levels) with diverse pulmonary and extra-pulmonary manifestations including variable clinical symptoms, natural history and longevity, physiology, imaging, and responses to therapy.
5. Most commonly, airflow obstruction/limitation is measured by spirometry by demonstrating a reduced FEV$_1$ : FVC ratio (Forced Expiratory Volume in one second : Forced Vital Capacity) [GOLD (Global initiative for chronic Obstructive Lung Disease) advocates a fixed ratio < 0.7, whereas others utilize a ratio < LLN (lower limit of normal, the 5th percentile of the population distribution of FEV$_1$ / FVC among nonsmokers with no clinical lung disease)].
6. Occasionally, COPD is diagnosed based upon radiographic findings of emphysema in the absence of airflow obstruction.
7. Definitions of COPD include:
   - GOLD Definition: COPD, a common, preventable, and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients.
   - ATS/ERS (American Thoracic Society/European Respiratory Society) Definition: Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking. Although COPD affects the lungs, it also produces significant systemic consequences.
1.1 Definition of Chronic Obstructive Pulmonary Disease (COPD)

The definition of COPD has evolved over the past several years. The most recent definitions of COPD by national and international groups are presented in Table 1.1. Key words in each of these definitions include: preventable, progressive, treatable, airflow obstruction that is not reversible [persistent], inflammation, lung/pulmonary, and exacerbation.

1.1.1 Preventable

As presented in Chapter 2, Epidemiology and Economic Consequences of COPD, and Chapter 9, Natural History, Phenotypes, and Gender Differences in COPD, tobacco smoke inhalation is the greatest risk factor for the development of COPD; approximately 75–90% of all individuals with COPD have been or are smokers, but only 20–50% of all smokers develop COPD. The factor(s) that place this subgroup of smokers at risk for the development of COPD are not known. Up to one quarter of individuals with COPD are non-smokers (Zeng, 2012). Other risk factors for the development of COPD include history of asthma or tuberculosis, exposure to traffic, outdoor pollution, and biomass smoke. Refraining from or quitting smoking (see Chapter 7, Smoking Cessation), and mitigating or avoiding chemical, dust, and fume exposure will prevent many individuals from developing COPD.

1.1.2 Progressive

Chapter 9, Natural History, Phenotypes, and Gender Differences in COPD, presents the longitudinal time course of lung function from birth to death. In healthy individuals, maximal physiologic function is achieved in the early 20’s and is followed by a slow reduction in flow rates measured by spirometry. COPD is characterized by an increased rate of decline in airflow. Although this accelerated decline is marked by parenchymal and airway derangements (including loss of lung tissue in emphysema, excessive airway mucous and inflammatory cell accumulation in chronic bronchitis), COPD can also be considered pulmonary physiologic progeria. This concept is captured by the term “lung age” (Reviewed in Chapter 4, Pulmonary Function Testing: Presence and Severity of Airflow Limitation/Obstruction). Lung age is the physiologic age of the lungs extrapolated from the normal predicted values of lung function based upon age and is compared with an individual’s chronologic age to illustrate the accelerated decline in lung function that occurs with COPD. For example, a 60 year old individual with significant airflow limitation might have spirometry (forced expiratory volume in one second (FEV$_1$) and forced vital capacity (FVC)) that would be normal for a 90 year old; thus, this person has a lung (physiologic) age of 90 but is only 60 years old chronologically. The progressive loss of lung function is heterogeneous and the
rate of decline is variable (Vestbo, 2014). (See Chapter 9, Natural History, Phenotypes, and Gender Differences in COPD for a discussion of lung development and the natural history of COPD.) Some interventions, especially early smoking cessation, may be associated with improvement in lung function and a reduction of the loss in years of life that occurs with persistent smoking (Jha, 2013). The effect of exacerbations on lung function decline appears to be less than previously thought, only 2 ml/yr/exacerbation in the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) study, whereas the mean rate of decline in the FEV$_1$ among participants with COPD was 33 ml/yr (Vestbo, 2011). In addition, ECLIPSE showed that not everyone with COPD experiences progressive decline in lung function measured by FEV$_1$; approximately 15% of participants with COPD had improvements in FEV$_1$, averaged over 3 years. All ECLIPSE participants were treated for COPD so it remains unclear whether the disease management affected the measured rate of decline or contributed to the improvement in lung function in these patients.

1.1.3 Treatable

As reviewed in Chapters 14, 16, and 17 Management of Stable COPD, Outpatient Management of COPD Exacerbations, and Inpatient Management of COPD Exacerbations, COPD is a treatable disorder. Current treatments have significant salubrious benefits...
and reduce the frequency and severity of exacerbations, improve the quantity and quality of life by reducing mortality, decreasing healthcare utilization, and improving health related quality of life. Previously many clinicians and patients had a nihilistic approach to COPD and considered it a self-inflicted, untreatable condition; this approach to COPD has changed dramatically in recent years. Individuals with COPD who receive optimal management can and do live longer with better quality of life.

1.1.4 Airflow Obstruction That Is Not Reversible [Persistent]

Airflow limitation is a reduction in expiratory airflow that occurs due to increased resistance to flow and reduced lung parenchymal elastic recoil. Airflow limitation is measured by spirometry (see Chapter 4, Pulmonary Function Testing: Presence and Severity of Airflow Limitation/Obstruction).

1.1.5 Major Point of Confusion: “Reversibility”

The term reversible has caused significant confusion among clinicians and has muddled the distinction between asthma and COPD. During pulmonary function testing, a response to bronchodilators is often termed “reversible airflow obstruction”. Bronchodilator responsiveness is determined by a ≥12% and ≥200 ml increase in either the FEV₁ or the FVC (ATS criteria, see Table 1.2). The intraday variation in FEV₁ and FVC is minimal in individuals with no lung disease and a change greater than 5–10% is considered significant (Dawson, 1965; Rozas, 1982). In patients with obstructive lung disease, the daily variation is greater and a significant change is 8–17% (Rozas, 1982; Pennock, 1981; Nickerson, 1980). [Interestingly, although the minimal clinically important difference for a change in FEV₁ in individuals with COPD is not known, a FEV₁ change of 100 ml can be perceived by most patients with COPD (Donohue, 2005).]

“Reversibility” is not a normalization or return to predicted levels of either the FEV₁ or FVC but simply a measured response (an increase in either FEV₁ or FVC) to a bronchodilator that exceeds the defined threshold. In individuals with COPD, airflow obstruction may improve after treatment with a bronchodilator but measures of airflow, FEV₁ and FVC, do not improve to a normal or predicted level. Depending upon the definition of bronchodilator responsiveness or “reversibility”, underlying lung function, the dose, type, and route of bronchodilator administration, between 38% and 73% of individuals with COPD may respond to bronchodilators with increases in FEV₁ or FVC (Hanania, 2011). Thus, COPD is characterized by airflow limitation that may improve after treatment with a bronchodilator but does not improve to a normal or predicted level. In contrast, in asthma, one expects measures of airflow to return to normal or predicted levels in all patients except for that subset of asthmatics
who have developed fixed airflow limitation. Spirometry testing in this group of asthmatics is indistinguishable from patients with COPD. A response to a bronchodilator should not be equated with normalization of lung function.

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition/Clarification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchodilator responsiveness</td>
<td>a &gt;12% and &gt;200 ml increase in either the FEV1 or the FVC after inhalation of a bronchodilator (usually a short acting beta agonist)</td>
</tr>
<tr>
<td>Normalization of airflow limitation</td>
<td>a return to predicted levels of FEV1 or FVC</td>
</tr>
<tr>
<td>“Reversibility”</td>
<td>a confusing term which should not be used</td>
</tr>
</tbody>
</table>

Thus, although bronchodilator response has been used in the past to distinguish COPD and asthma, recent evidence and the large proportion of patients with COPD who respond to bronchodilators demonstrate that the acute spirometric response to bronchodilators cannot be used to distinguish asthma from COPD (Chhabra, 2005). The response to bronchodilators is used to define a subgroup (phenotype) of individuals with COPD who may respond better to inhaled corticosteroids (see Chapter 9, Natural History, Phenotypes, and Gender Differences in COPD).

1.1.6 Inflammation

COPD is characterized by an inflammatory reaction within the lung to inhaled particles or gases and this response may be triggered by activation of both innate and adaptive immune responses (Angelis, 2014; Rovina, 2013). Inflammatory markers are present both systemically as well as within the lung. Chapter 6, COPD Pathogenesis: Etiology and Systemic Inflammation, discusses the etiology and pathophysiologic pathways that are activated in COPD. Recent studies have shown that the inflammation in COPD is not limited to the lungs but occurs systemically and may play a role in the multisystemic manifestations of COPD (see Chapter 10, COPD Is a Multi-organ Disorder: Systemic Manifestations). However, the presence of systemic inflammation does not occur universally among individuals with COPD. The ECLIPSE study showed that about one third of participants with COPD never demonstrated systemic inflammation, 16% had persistent elevation of systemic inflammatory markers, and most participants had evidence of variable systemic inflammation (Agusti, 2012). The regulatory mechanisms that control the development of pulmonary and systemic inflammation in individuals with COPD are not well defined presently. These inflammatory processes are the subject of intense study to develop new therapeutics that interdict the development and consequences of inflammation in COPD.
1.1.7 Lung/Pulmonary

COPD is classically considered a pulmonary disorder; however, recent evidence over the past 10 years shows that COPD pathophysiology may extend beyond the lungs and affect other organ systems (see Chapter 10, COPD Is a Multi-organ Disorder: Systemic Manifestations). COPD is also associated with significant psychosocial manifestations that may intensify an individual’s reaction to the sensation of breathlessness and profoundly influence their disease manifestations and course (Reviewed in Chapter 13, COPD's Effects on Psychosocial Functioning and Familial Interactions). The breathlessness and exertional limitations caused by COPD may increase the reliance upon others while simultaneously restricting and diminishing familial and social interactions for patients with COPD. Finally, COPD affects other systems including the pulmonary vasculature (see Chapter 12, COPD and Pulmonary Vasculature) and sleep (see Chapter 11, COPD and Sleep: Overlap Syndrome).

1.1.8 Exacerbation

The clinical course of COPD is punctuated by exacerbations, episodes of symptom worsening beyond their normal day to day variation that occur after a period of recovery from a prior exacerbation (Triqueros, 2013). COPD exacerbations are often triggered by respiratory infections and are the leading cause of healthcare utilization and cost in the management of COPD (see Chapters 16 and 17 on the management of COPD in the outpatient and inpatient settings). One of the major advancements in COPD management over the past two decades has been the development of treatments that reduce the number and severity of COPD exacerbations.

1.2 Diagnostic Criteria

Until recently, the sine quo non for the diagnosis of COPD has been the presence of airflow limitation, a reduction in the flow of air from the lungs during exhalation due to increased airway resistance and dynamic airway collapse (see Chapter 4, Pulmonary Function Testing: Presence and Severity of Airflow Limitation/Obstruction). How airflow limitation is defined, measured, and quantified have evolved over the past several decades. Airflow limitation is currently measured by the ratio of FEV\textsubscript{1} to FVC and is defined when this ratio is less than a threshold value. The two most common thresholds are an absolute value of 0.7 and the lower limit of normal, the 5\textsuperscript{th} percentile of the distribution of the FEV\textsubscript{1}/FVC ratio in a nonsmoking population with no clinical evidence of lung disease. Because the ratio of FEV\textsubscript{1}:FVC decreases with age, use of an absolute threshold may be overly sensitive and may over-diagnose airflow obstruction in older individuals and under-diagnose younger people (see
Introduction and Definition of Chronic Obstructive Pulmonary Disease COPD

Chapter 4, Pulmonary Function Testing: Presence and Severity of Airflow Limitation/Obstruction. More individuals with airflow obstruction defined by fixed ratio have emphysema and gas trapping than those who have airflow obstruction defined by the lower limit of normal (Bhatt, 2014).

Recent findings suggest that some individuals with radiographic evidence of emphysema, gas trapping, regional ventilation derangements, and airway alterations may not have airflow limitation on physiologic testing (Coxson, 2014), (see Chapter 5, Radiology: Use of lung imaging to help in the identification of patients with COPD.) Recently developed advanced pulmonary imaging techniques such as x-ray computed tomography, magnetic resonance imaging, and use of hyperpolarized noble gases provide structural as well as functional assessments of the lungs that may detect earlier and more subtle changes than can be measured by spirometry. Thus, although the presence of physiologic airflow limitation is currently a critical criterion for the diagnosis of COPD, it may not be essential as newer lung imaging techniques are developed and become more universally available.

1.3 Staging Disease Severity

Traditionally COPD has been categorized and staged based upon spirometry measurements. Airflow severity is determined by the comparison between the measured FEV₁ and the predicted FEV₁, the FEV₁% of predicted value, and is segregated into several categories ranging from mild to very severe (see Chapter 4, Pulmonary Function Testing: Spirometry: Presence and Severity of Airflow Limitation/Obstruction). These divisions are artificial as the reduction in lung function is a continuum from normal to severely deranged.

Previous COPD staging schemes were based solely upon airflow severity. With the realization that airflow severity does not correlate well with disease course, clinical outcomes, health status, or disease management, multivariate staging methods have been proposed (Jones, 2009). One of the more recent and widely adopted schemes is the GOLD staging classification which utilizes three variables: airflow severity, respiratory symptoms measured by the COPD Activity Test or mMRC (modified Medical Research Council) dyspnea scale, and the number of COPD exacerbations within the previous year (see Chapter 14, Management of Stable COPD). Other multifactorial indices include BODE (Body mass index, airflow Obstruction, Dyspnea, and Exercise capacity), ADO (Age, Dyspnea, and airflow Obstruction), and DOSE (Dyspnea, Obstruction, Smoking, and Exacerbation) (Celli, 2004; Puhan, 2009; Jones, 2009). The goals of these multivariate staging classifications are to provide COPD categories that are more clinically useful and assist with disease management and prognostication (see Chapter 19, Integrating Supportive, Palliative, and End of Life Care for COPD).
1.4 COPD is a Syndrome

Historically, COPD has been considered an overlapping dyad of pulmonary disorders characterized by airflow obstruction and different clinical, radiographic, and physiologic manifestations: chronic bronchitis and emphysema, that are distinguished from asthma, the other major cause of airflow obstruction (Table 1.3).

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic bronchitis</td>
<td>the presence of a productive cough for at least 3 consecutive months in 2 consecutive years</td>
</tr>
<tr>
<td>Emphysema</td>
<td>an abnormal enlargement of the air spaces distal to the terminal bronchioles accompanied by destruction of their wall and without obvious fibrosis pathologically or radiographically</td>
</tr>
</tbody>
</table>

More recent COPD studies have focused on further refinement and definition of COPD categories or phenotypes (see Chapter 9, Natural History, Phenotypes, and Gender Differences in COPD). The ECLIPSE study is a 3 year prospective investigation of 2,164 patients with clinically stable COPD, 337 smokers with normal lung function, and 245 never smokers that has provided valuable insights into the heterogeneity of COPD and its variable and not always progressive course. Among the COPD phenotypes identified in ECLIPSE are frequent (≥ 2 yearly) exacerbators and infrequent (<2 yearly) exacerbators, those experiencing a more rapid decline in FEV\textsubscript{1} (continued smokers, CT defined emphysema, and bronchodilator responsiveness), greater loss of lung density/parenchyma (smokers and women), bronchodilator responsiveness (more frequent exacerbators, although bronchodilator responsiveness was variable throughout the study), and systemic inflammation (approximately one third of patients with COPD never demonstrated evidence of systemic inflammation and 16% had persistent systemic inflammation with a 6-fold increase in overall mortality) (Augusti, 2012; Vestbo, 2014).

1.5 Genetic Factors

Only a minority of tobacco smokers develop COPD and the genetic risk factors for the development of COPD are not known. Mutations in the alpha-1-antitrypsin gene are associated with the development of emphysema and have been well characterized and replacement therapy is available. More recently, large multicenter investigations have used genome-wide association studies of populations that are clinically,
Introduction and Definition of Chronic Obstructive Pulmonary Disease COPD

Physiologically, and radiographically well characterized to identify potential genetic loci associated with the development of COPD and with different COPD phenotypes (Chen, 2013; Cho, 2012; Bosse, 2012; Berndt, 2012). Other studies have focused on epigenetics (heritable variations that alter gene expression but do not change the DNA sequence) such as DNA methylation, histone alteration, and RNA-associated silencing, and their role in the development of COPD (Mortaz, 2011).

1.6 Clinical Symptoms and Differential Diagnosis

The three major symptoms associated with COPD are breathlessness, cough, and sputum production (see Chapter 3, COPD Recognition and Diagnosis: Approach to the Patient with Respiratory Symptoms, and Chapter 14, Management of Stable COPD.) Breathlessness is a subjective sensation of shortness of air that is normally experienced by everyone during vigorous or strenuous activity. With COPD, the initial manifestations may be subtle; an inability to maintain the pace when walking with peers or increased sensation of breathing while doing routine activities to overt wheezing and gasping for breath during activities. Cough is the forceful exhalation of air to clear the airways from irritating or obstructing material. Cough may be nonproductive or productive of phlegm. These symptoms are neither sensitive nor specific for the diagnosis of COPD and must be interpreted in conjunction with the clinical history and laboratory and radiographic findings (see Chapter 5, Radiology: Use of lung imaging to help in the identification of patients with COPD).

The differential diagnosis of COPD includes asthma, congestive heart failure, bronchiolitis, pulmonary infections, and bronchiectasis. Some distinguishing features between COPD and asthma are presented in Table 1.4. Thus, even though COPD and asthma are characterized by airflow limitation, they are distinct disorders with very different pathophysiologic mechanisms that lead to different and distinct treatment regimens. Nevertheless, in some patients it may not be possible to distinguish asthma and COPD despite extensive evaluation and this undifferentiated group is now classified as asthma COPD overlap syndrome. Many other

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Asthma</th>
<th>COPD</th>
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<tr>
<td>Anatomic Distribution</td>
<td>Small airways</td>
<td>Small airways</td>
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<td></td>
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<td>Parenchyma</td>
</tr>
<tr>
<td>Cells</td>
<td>Eosinophil predominant</td>
<td>Neutrophil predominant</td>
</tr>
<tr>
<td>Cytokines</td>
<td>CD4 Th2: IL-4, IL-5, IL-9, IL-13</td>
<td>CD8 Th1: IFN g</td>
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Table 1.4: Distinguishing features between COPD and asthma
disorders may occur concurrently with COPD and it may be difficult to discern the primary process. See Chapter 3, COPD Recognition and Diagnosis: Approach to the Patient with Respiratory Symptoms, for a detailed discussion of the differential diagnosis of COPD and assessment of patients presenting with breathlessness, cough, and sputum production.

1.7 Imaging

The chest x-ray may demonstrate hyperinflation with reduced peripheral vascular markings, flattening of the diaphragms, and a central and narrowed cardiac silhouette in individuals with emphysema. Although these findings are sensitive for the presence of COPD, they are not specific (Washko, 2012). Chest CT provides more detailed images of the lung parenchyma, airways, and vasculature. Chest CT imaging is commonly used for the diagnosis of emphysema and may be quantified by various densitometric analyses that demonstrate the loss of lung parenchyma. In addition, chest CTs may be used to measure central and peripheral small airway wall thickness, caliber, and number. More recent studies using micro-CT techniques have demonstrated that COPD is associated with reduced numbers of airways as well as pulmonary vessels in the lung parenchyma (Washko, 2012). Chapter 3 presents a more detailed review of the radiographic findings in COPD.

1.8 Treatment

Recent advances in the management of COPD have led to reductions in respiratory symptoms, improvements in quality of life, fewer exacerbations and less hospitalizations, and better survival for individuals with COPD. Chapter 8, Fostering Patient Self-Management of COPD reviews how providers may approach patients with COPD and encourage them to participate actively in their disease management; Chapter 7, Smoking Cessation, discusses smoking cessation, the single most important intervention for the prevention and management of COPD; treatment of stable COPD and exacerbations are reviewed in Chapters 14, 16, and 17, Management of Stable COPD, Management of Outpatient COPD Exacerbations, and Management of Inpatient COPD Exacerbations. Optimal COPD management is interdisciplinary and the role of primary care providers and their interaction with other providers is discussed in Chapter 18, Primary Care and Interaction with Specialty Care for the COPD Patient. Finally, advanced care planning is presented in Chapter 19, Integrating Supportive, Palliative, and End of Life Care for COPD.
1.9 Conclusion

COPD is a complex disorder with protean manifestations that are not limited to the lungs. Although, COPD has been classified historically as chronic bronchitis, emphysema, or a combination of these two processes, more recent research has identified a plethora of COPD phenotypes with varying clinical, radiographic, genetic, and biochemical characteristics with distinct prognostic and therapeutic implications. Thus, COPD is clearly a universe of different disorders that we are just beginning to understand and differentiate. The clinical application of these phenotypes and their use in management has begun with the utilization of classification and management guidelines that extend beyond the physiologic characterization of patients to include symptom severity and exacerbation risk. Further studies will identify other clinical, biochemical, physiologic, and radiographic variables that are critical to the characterization and classification of COPD and to better and more precisely directed management strategies.

1.10 Summary Points

1. The definition of COPD has evolved and continues to change with further clinical, genetic, biochemical, and radiologic studies.
2. Although COPD has historically been defined by airflow obstruction measured by spirometry, physiologic impairment is only one aspect of this disorder and does not correlate perfectly with disease severity, quality of life, or management.
3. COPD is a plethora of diverse phenotypes that are becoming better defined and characterized; these phenotypes are beginning to define more specific treatment regimens.

References


Ralph J. Panos, MD

2 Epidemiology and Economic Consequences of COPD

Key Points
1. Tobacco smoke inhalation is the major risk factor for the development of COPD.
2. Secondhand, passive, or environmental tobacco smoke exposure may also have a potentially important role in the development of chronic lung disease.
3. Approximately one quarter of individuals with COPD are not smokers; nontobacco smoke risk factors for COPD development include indoor and outdoor air pollutants, workplace dust and fumes, childhood lower respiratory disorders including asthma, and pulmonary infections (tuberculosis and human immunodeficiency virus).
4. Chronic lower respiratory disease (COPD and asthma) is the third leading cause of death in the US.
5. In 2010, the total cost of COPD in the US was estimated to be $36 billion and is projected to rise to $49 billion in 2020.
6. The majority of COPD medical costs are related to healthcare visits (emergency department and hospitalizations) for exacerbations.
7. COPD impairs workers and is a significant contributor to sick and disability leave and employer healthcare costs.

2.1 Introduction

Studies of the epidemiology of COPD provide critical associations between environmental risk factors and the development of airflow limitation and other disease manifestations in vulnerable individuals. Obstructive lung disease does not develop in all individuals exposed to known potential risk factors which suggests that, in addition to environmental exposures, a genetic predisposition or susceptibility is required for the development of COPD. Because the hereditary factors (other than alpha 1 antitrypsin mutations) are poorly characterized, these epidemiologic associations provide the best current opportunity to prevent the development of COPD by identifying potentially avoidable exposures and decreasing their detrimental effects.

COPD may be the single most underdiagnosed and misdiagnosed chronic disorder with the greatest economic consequences (Mannino, 2002; Mannino, 2007; Diaz-Guzman, 2014). COPD is the third leading cause of death in the US and accounts for nearly $40 billion dollars in direct healthcare costs with approximately additional $4 billion dollars in indirect costs due to lost or impaired work (Ford, 2014). An analysis of the National Health and Nutrition Examination Survey 2007–2009 revealed COPD under-diagnosis (failure to diagnose COPD in individuals with respiratory symptoms
and airflow limitation measured by spirometry) of 82.9% (95% confidence interval (CI) 75.2, 88.6) and over-diagnosis (diagnosis of COPD in individuals who did not have airflow limitation) of 61.1% (95% CI, 49.0, 72.0) (Munson, 2013). Other studies suggest that the under-diagnosis of COPD ranges from 63.3–71.1% (Murphy, 2011; Mannino, 2000; Petty, 2000).

COPD exacerbations including emergency room visits and hospitalizations are the major factors contributing to direct medical costs of COPD (Darnell, 2013). Nearly three quarters of individuals diagnosed with COPD are under 65 years old and employees spend about $17,000 per year on employees with COPD which is three times more than for those who do not have COPD (Bunn, 2008).

Despite COPD’s significant economic costs and prevalence, research support for COPD basic science, translational, and clinical studies is severely underfunded. An analysis of National Institutes of Health research funding for 29 common conditions found that COPD was the most underfunded disorder based upon disease burden (Gillum, 2011).

### 2.2 Epidemiology

#### 2.2.1 Risk Factors for COPD Development

**2.2.1.1 Tobacco Smoke**

Although tobacco smoke inhalation is the major factor associated with the development of COPD globally, smoking is the predominant risk factor in the developed world and other factors dominate in the developing world currently. A large meta-analysis of 218 studies examining the relationship between smoking and COPD, chronic bronchitis, and emphysema revealed a relative risk (RR) of ever smoking and developing COPD of 2.89 (95% CI 2.63, 3.17), chronic bronchitis 2.69 (95% CI 2.50, 2.90), and emphysema 4.51 (95% CI 3.38, 6.02) (Forey, 2011). For current smokers, the RR increases to 3.51 (95% CI 3.08, 3.99) for COPD, to 3.41 (95% CI 3.13, 3.72) for chronic bronchitis, and to 4.87 (95% CI 2.83, 8.41) for emphysema. The risk for lung disease increased with the amount and the duration of smoking, and decreased with increasing age of starting to smoke and duration of smoking cessation (Forey, 2011). The effect is greater for cigarette smokers and less for pipe and cigar smokers. In addition, the age of smoking cessation significantly influences the effect of smoking on longevity (Jha, 2013). Quitting smoking by the age of 35 neutralizes most of the excess mortality due to smoking (Jha, 2013). Smoking cessation reduces the rate of lung function decline at all stages of COPD but has the greatest effect in early disease (Welte, 2014). Thus, the amount, duration, age of starting smoking, age of quitting smoking, duration of smoking abstinence, and type of tobacco product all contribute to the development of COPD.
2.2.1.2 Passive or Environmental Tobacco Smoke Exposure

The 2006 Surgeon General’s report concluded that secondhand, passive, or environmental tobacco smoke exposure is associated with multiple disorders including COPD, asthma, respiratory infections, cardiovascular disease, and cancer but the evidence was insufficient to establish a causal relationship (U.S. Department of Health and Human Services, 2006). Environmental tobacco smoke exposure includes 85% sidestream smoke from the burning tip of a cigarette and 15% mainstream smoke that is exhaled by an active smoker (Manuel, 1999). Sidestream smoke is unfiltered and contains smaller particles than mainstream smoke but both sources contain multiple toxic and carcinogenic agents (Reardon, 2007).

Passive smoke exposure in utero or during early childhood may adversely affect lung development and predispose to the subsequent development of COPD (Stocks, 2013), (discussed in Chapter 9, Natural History, Phenotypes, and Gender Differences in COPD.) Among nonsmoking adults over the age of 40 in China, over 78% had environmental tobacco smoke exposure and the odds of COPD among those with home or work environmental tobacco smoke exposure is 1.48 (95% CI, 1.18, 1.85) (Regional COPD Working Group, 2003; Yin, 2007). A meta-analysis of the effect of second hand smoke exposure and the development of COPD shows an increased odds ratio (OR) of 1.56 (95% CI 1.40, 1.74) (Eisner, 2010). Workers in environments where laws have been enacted prohibiting smoking experience less cough and phlegm production and their lung function improves after smoking has been banned from their workplace (Goodman, 2007; Menzies, 2006; Eagan, 2006).

2.2.1.3 Non-tobacco Smoke Factors

The attributable risk for the development of COPD due to tobacco smoke ranges from 9.7 to 97.9% but is generally less than 80%, which suggests that other exposures contribute to 20% or more of COPD cases (Eisner, 2010). Approximately one quarter of individuals with COPD in the US, UK, and Spain were never smokers (Salvi, 2009). Factors other than tobacco smoke that have been associated with the development of COPD include indoor and outdoor air pollutants, workplace dust and fumes, childhood lower respiratory infections, pulmonary tuberculosis, chronic asthma, intrauterine growth retardation, poor nutrition, and lower socioeconomic status (Salvi, 2009; Eisner, 2010; Diaz-Guzman, 2012). Depending upon the level of these exposures, between 25 and 45% of individuals with COPD may be never smokers (less than 100 cigarettes in their lifetime) (Salvi, 2009).

2.2.1.4 Occupational Exposures

Combined tobacco smoke and occupational exposures to dusts, gases, fumes, and smoke significantly increase the risk of developing COPD (Blanc, 2009; Salvi, 2009; Eisner, 2010; Doney, 2014; Omland, 2014). In the US, approximately 15% of cases of
COPD may be due to environmental exposures in the workplace when controlling for tobacco smoke exposure (Balmes, 2003; Blanc, 2007). Between 30–40% of farmers have COPD and lung disease is associated with ammonia and dust inhalation (Lamprecht, 2007; Eduard, 2009). Dust exposure, especially from silica, is associated with COPD among construction workers, miners, and foundry and concrete workers (Salvi, 2009). Other industries with increased risk of COPD include plastics, textile, rubber, leather, trucking (especially with diesel exhaust exposure), and food products (Salvi, 2009; Hnizdo, 2002; Weinmann, 2008).

2.2.1.5 Air Pollution

2.2.1.5.1 Indoor
Exposure to biomass fuels (wood, dung, and coal) that are used in open fire stoves throughout the developing world is a significant risk for the development of lung disease, especially among nonsmoking women and children (Regalado, 2006; Rinne, 2006; Grigg, 2009). Worldwide, approximately 50% of all and 90% of rural households use biomass fuels for heating and cooking (Zeng, 2012). Biomass smoke exposure increases the odds for developing COPD by two to three fold (Sood, 2012). A systematic review of the association between solid fuels and COPD and chronic bronchitis demonstrated OR’s of 2.80 (95% CI 1.85, 4.0) and 2.32 (95% CI 1.92, 2.80), respectively (Kurmi, 2010). In addition, solid fuel smoke is associated with increased lung infections, especially among women and children, higher risk for asthma, interstitial lung disease, and lung cancer (Sood, 2012).

2.2.1.5.2 Outdoor
Outdoor air pollution is associated with impaired development of lung function in childhood and adolescence which may reduce peak lung function or decrease the duration of the plateau phase of maximal lung function (see Chapter 9. Natural History, Phenotypes, and Gender Differences in COPD.) (Gauderman, 2004; Gauderman, 2007; Rojas-Martinez, 2007; Ko, 2012). The Study on the Influence of Air Pollution on Lung Function, Inflammation, and Aging (SALIA) showed that increasing exposure to aerosolized particulate matter was associated with reductions in FEV₁, FVC, and FEV₁/FVC and increased risk for COPD in 4,575 German women (Schikowski, 2005). The Swiss Study on Air Pollution and Lung Diseases in Adults demonstrated a reduction in the decline in lung function as air quality improved (Downs, 2007). In the UK, the lung function of postmen working in cities with worse air pollution is reduced compared to those working in areas with better air quality (Fairbairn, 1958; Holland, 1965). In addition, worse air pollution is associated with increased COPD exacerbations; for every 10 microgram/m³ increase in the annual mean particulate matter 10, (PM10 >100 microgram/m³), the hospitalization rate for acute COPD exacerbations increases by 2.4% (Ko, 2007).
2.2.1.6 Sex
Women appear to be more susceptible to the development of smoking related COPD (Aryal, 2014). They develop greater airflow limitation at younger ages and with less tobacco smoke exposure, experience a faster rate of lung function decline than men, and have a higher risk of hospitalization for acute exacerbations of COPD (Aryal, 2014; Gan, 2006, Tam, 2013). Potential explanations for the gender differences in COPD manifestations include dysanapsis (airway size disproportionate to lung size; women’s airways are smaller than men’s even controlling for differences in lung size), elevated susceptibility to inflammation and mucus hypersecretion, differential effects of hormones, differences in pulmonary particle deposition, and greater and longer cigarette smoke inhalation by women compared with men (Tam, 2013).

2.2.1.7 Infections
Review of epidemiologic studies of tuberculosis (TB) and COPD demonstrate an increased risk of obstructive lung disease in individuals who previously had pulmonary tuberculosis with OR between 1.37 and 2.94 (Allwood, 2013; Ehrlich, 2011). The prevalence of COPD among individuals previously treated for tuberculosis ranges from 28–68% and increases with the time after tuberculosis treatment completion (Jordan, 2010). Prior tuberculosis infection is associated with accelerated lung function decline but it is unclear if the pathophysiology of this reduction is related to the processes that cause lung function decline in tobacco-related COPD (Hnizdo, 2000). Conversely, smoking doubles the risk of TB infection, active disease, and mortality (van Zyl-Smit, 2010).

Human immunodeficiency virus (HIV) infection is another risk factor for COPD, especially emphysema (Raynaud, 2011; Gingo, 2013). Early reports associated HIV infection with air trapping, reduced diffusing capacity, and CT scan evidence of emphysema (Diaz, 1992; Diaz, 2000). When controlling for smoking, HIV infected individuals older than 50 years have an 11% higher incidence of COPD than those who are not infected and, among those less than 50 years old, the incidence is 25% greater (Crothers, 2011). HIV infected injection drug users are 3.4 fold more likely to have obstructive lung disease than non-infected users (Drummond, 2012). Smoking further increases the risk of COPD among HIV infected individuals (Crothers, 2005).

2.2.2 Prevalence

2.2.2.1
The measurement of COPD prevalence is extremely dependent upon the criteria used to define COPD, use of spirometry, and the threshold for airflow limitation. Many epidemiologic studies utilize a clinical definition of COPD asking participants if they have ever been told by a healthcare provider that they have COPD, chronic bronchitis,
or emphysema. In the absence of physiologic measurement, the clinical diagnosis of COPD may be inaccurate in 25% of patients (Murray, 2011). Even when spirometry is used, the measured prevalence will depend upon whether pre-bronchodilator or post-bronchodilator values are used to determine the presence of airflow limitation. The threshold for the definition of airflow limitation significantly alters the measured prevalence of airflow limitation (discussed in Chapter 4, Pulmonary Function Testing: Presence and Severity of Airflow Limitation/Obstruction). Even studies that used very standardized and uniform methodologies such as the Burden of Obstructive Lung Disease (BOLD) and the Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO) found dramatic variability in COPD prevalence across countries and regions (Buist, 2007; Menezes, 2005). Therefore, when reviewing studies of COPD epidemiology, one should be careful to assess study methodology and disease definitions.

Because tobacco smoke inhalation is the predominant cause of COPD, the prevalence of COPD corresponds closely with smoking rates but with a lag of several decades. In the US, smoking rates for men peaked in the 1950s and 1960s and COPD prevalence and mortality rates have stabilized or begun to decline (http://www.tobaccoatlas.org/products/male_tobacco_use/prevalence/; http://www.cdc.gov/copd/data.htm). For women, smoking rates peaked in the 1970s and 1980s and the prevalence and mortality rates of COPD in women more than doubled from 1980 to 2000 and have stabilized from 1999 to 2010 (http://www.tobaccoatlas.org/products/female_tobacco_use/prevalence/; http://www.cdc.gov/copd/data.htm). Thus, where cigarette smoke inhalation is the predominant cause of COPD, the prevalence of COPD lags smoking rates by several decades.

2.2.2.2 United States

2.2.2.2.1 Prevalence
Based upon the National Health Interview Survey, 5.1% of US adults over the age of 18 had COPD in 2007–2009 and the prevalence of COPD was greater in women, 6.1%, than in men, 4.1% (Akinbami, 2011). The overall prevalence of COPD was stable from 1998 through 2009. COPD prevalence increased with age and was higher in women than in men throughout most age groups.

The Third National Health and Nutrition Examination Survey (NHANES III) estimated that the prevalence of COPD was 6.8–8.5% within the general US population (Mannino, 2000). COPD prevalence was estimated to be greater in current (12.5%) and former (9.4%) smokers than in never smokers (5.8%) (Mannino, 2000). In 2011, 6.8% of US adults older than 25 years reported that a caregiver had told them that they had COPD (Ford, 2013). The age adjusted prevalence was higher in American Indian/Alaska natives, 11.0%, than in non-Hispanic whites, 6.9%, non-Hispanic blacks, 5.7%, Hispanics, 4.1%, and Asian/Pacific Islanders, 2.5%. COPD prevalence was also
greater in women, 7.3%, than in men, 5.7% (Ford, 2013). Geographically, COPD prevalence was greatest in the states bordering the Ohio and Mississippi Rivers (Ford, 2013).

### 2.2.2.2 Gender Distribution

Over the past decade several dramatic changes in the gender distribution of COPD have occurred in the US (Ohar, 2011). For the first time in 2000, more women than men died from COPD in the US (Arias, 2003). Female smokers are 13 times more likely to die from COPD than nonsmoking women whereas male smokers are 12 times more likely to die from COPD than nonsmoking men (U.S. Department of Health and Human Services, 2014). Women are twice as likely to be diagnosed with chronic bronchitis as men; in 2011, 56.7 women per 1,000 population were diagnosed with chronic bronchitis compared with 29.6 per 1,000 population among men (http://www.lung.org/lung-disease/copd/resources/facts-figures/COPD-Fact-Sheet.html). Also, in 2011, the prevalence of diagnosed emphysema was greater in women than in men, 21.4 per 1,000 compared to 19.0 per 1,000. (http://www.lung.org/lung-disease/copd/resources/facts-figures/COPD-Fact-Sheet.html).

### 2.2.2.3 Healthcare Utilization and Occupational Consequences

In the 2011 Behavioral Risk Factor Surveillance System survey, 6.3% of US had a self-reported caregiver diagnosis of COPD (Centers for Disease Control and Prevention, 2012). Of those with COPD, 76.0% had undergone pulmonary function testing, 64.2% felt their quality of life was impaired by breathlessness, and 55.6% were taking at least one breathing medication. In the year before the survey, 43.2% had seen a physician and 17.7% had been seen in an emergency room or hospitalized for respiratory-related symptoms. In 2010, there were 495 physician office visits, 72 emergency department visits, and 34 hospitalizations with a primary diagnosis of COPD per 10,000 US population (Ford, 2013).

Analysis of data from the National Health and Wellness Survey of over 20,000 employed US adults between 40 and 64 years old revealed that 5.5% self reported a diagnosis of COPD (DiBonaventura, 2012). Those with COPD reported greater presenteeism (the percentage of impairment while at work due to health in the past 7 days), and overall work and daily activity impairment.

### 2.2.2.4 Mortality

In 2007, nearly 60,000 men (63.5 per 100,000 population) and nearly 65,000 women (46.8 per 100,000 population) died from COPD. The death rates from COPD declined for men but did not change for women from 1999 through 2007. Lower respiratory disease (COPD and asthma) was the third leading cause of death in the US in 2008 (Minino, 2010). COPD was the primary cause of approximately one in every 20 deaths in the US in 2005 (CDC, 2008).
2.3 Economics

2.3.1 Direct Costs

Direct costs are the expenses incurred by the healthcare system, community, and patients and their families due to illness. The total US costs related to COPD and its comorbidities in 2010 are estimated to be $36 billion with $32.1 billion due to direct medical expenditures and $3.9 billion in indirect or absenteeism costs (Ford, 2014). By 2020 the national direct medical costs of COPD are predicted to rise to $49 billion (Ford, 2014). COPD exacerbations and their management account for 45–75% of direct costs (Toy, 2010). A summary of the costs of COPD in 2006 estimated the per-patient direct costs to be $2,700-$5,900 annually with excess costs ranging from $6,100 to $6,600 annually (Foster, 2006). In 2008, hospitalization costs for COPD exacerbations were estimated to range from $7,242 for an uncomplicated admission to $44,909 for a complex admission requiring mechanical ventilation and critical care (Dalal, 2011). Medicare beneficiaries with COPD have annual healthcare costs $20,500 greater than those without COPD (Menzin, 2008). Overall healthcare costs are greater for those with COPD compared to individuals who do not have COPD.

Among 8554 patients with COPD, mean annual COPD related healthcare costs were $4069 overall but $6381 for patients with two or more exacerbations and mean all cause healthcare costs were $18,976 overall and $23,901 for those with two or more exacerbations (Pasquale, 2012). Higher costs occurred among those with more severe exacerbations, comorbid cardiovascular disease, diabetes, and supplemental oxygen use. A review of 58,589 patients with COPD in the United Kingdom showed that the annual cost of COPD care was 1,523, 2,405, and 3,396 pounds (approximately, $2303, $3637, and $5135, US dollars, respectively) for patients with 0, 1, and 2 or more exacerbations (Punekar, 2014).

Hospitalization costs for COPD increase with the severity of the exacerbation. Analysis of administrative data from 602 hospitals in 2008 revealed that hospitalizations requiring intensive care and intubation cost $44909 whereas ward hospitalization cost $7242; complex hospitalizations requiring either intubation or intensive care accounted for only 5.8% of COPD hospitalizations but 20.9% of hospitalization costs (Dalal, 2011). Other factors that may increase the cost of COPD hospitalizations include hospital acquired pneumonia, chronic renal failure, and anemia (Ornek, 2012).

Severity of disease measured by airflow obstruction correlates very positively with the cost of COPD-related healthcare costs (de Miguel diez, 2008). Analysis of direct healthcare costs due to COPD among 160 patients with COPD in Taiwan showed that annual costs increased with airflow obstruction severity, 38,203, 149,031, and 288,825 new Taiwan dollars (approximately $1193, $4657, and $9026 US dollars, respectively) for individuals with mild (FEV1% predicted >50%), moderate (FEV1% predicted <30% and <50%), and severe (FEV1% predicted <30%) disease and the greatest contributor to cost was hospitalization (Chiang, 2008). A Swedish review confirmed the strong
positive correlation between COPD severity and costs but suggested that over the past
decade, costs have decreased for those with more severe disease and increased for
individuals with more mild to moderate COPD (Jansson, 2013).

Comorbid conditions increase the healthcare cost for individuals with COPD (de
Miguel diez, 2008; Dalal, 2011; Perera, 2012; Nielsen, 2011). Acute coronary syndrome,
congestive heart failure, cerebrovascular disease, bronchogenic cancer, cardiac dys-
rhythmias, pulmonary vascular disease, and weight loss are associated with greater
costs and mortality (Perera, 2012). Patients with COPD and cardiovascular disease
have more ED visits (OR 1.47), more respiratory-related hospitalizations (OR 1.95), and
any hospitalization or ED visit (OR 1.62). The annual total healthcare costs were nearly
three-fold greater for those with COPD and cardiovascular disease compared with

2.3.2 Indirect Costs

Indirect costs are the economic output losses caused by illness. COPD is estimated to
cause 16.4 million days of lost work annually (Ford, 2014). Estimated mean annual
number of sick leave or disability days taken by employed individuals with COPD
due to respiratory symptoms range from 1.3 to 19.4 days with estimated costs of $893-
$2,234 per person (Patel, 2014). The type or amount of work performed by approxi-
mately 13–18% of individuals with COPD is limited and over one third experience
reductions in their general activities (Patel, 2014). The number of days with dimin-
ished activity ranges from 27–63 days and employed individuals with COPD utilize
between 1.3 and 19.4 days of sick or disability leave and may be bed bound for 13–32
days yearly (Patel, 2014). The annual indirect costs of COPD ranged from $1,521–3,348
per person in 2012 US dollars and comprised 27–61% of the total costs related to COPD
(Patel, 2014).

2.3.3 Effect of Treatment

Prescription and adherence with respiratory medications correlate inversely with
healthcare utilization for individuals with COPD. Yearly hospitalizations and emer-
gency department visits decreased by 2.5% and 1.8%, respectively, for every 5%
increase in proportion of days covered (a measure of the percentage of days during
which an individual filed claims for respiratory medications; it is an indirect epidemi-
ologic measure of medication adherence) whereas outpatient visits only increased by
0.2% (Toy, 2011). A retrospective analysis of over 55,000 patients with COPD showed
that medication adherence increased with less frequent dosing interval of respira-
tory medications; the proportion of days covered was 43.3%, 37.0%, 30.2%, and 23.0%
for once, twice, thrice, and four times daily regimens (Toy, 2011). The annual cost
of care for 1000 patients with COPD decreased by $300,000 for every 5% increase in adherence (Toy, 2011). In a retrospective review of 33,816 Medicare beneficiaries with COPD, medication adherence measured by medication continuity or proportion of days covered was associated with lower hospitalization rates (RR, 0.88) and less Medicare cost (-$3764) (Simoni-Wastila, 2012). In addition, patients with a proportion of days covered greater than 80% had less hospitalizations (RR 0.90) and lower cost (-$2185) than those with less than 80% of days covered (Simoni-Wastila, 2012). An analysis of maintenance medication use versus no maintenance medication use among 6322 Medicare beneficiaries demonstrated that the users had fewer hospitalizations (OR 0.70, 95% CI, 0.61–9.79), rehospitalizations (OR 0.74, 95% CI 0.63–0.87) and lower Medicare costs (-$3916, 95% CI, -$4977,-$2854) (Stuart, 2010).

Integrated disease management programs for COPD that incorporate two or more interdisciplinary healthcare providers and two or more treatment components reduce respiratory-related hospitalizations and length of stay and improve respiratory quality of life and exercise capacity (Kruis, 2013). A VHA COPD disease management program produced an average cost savings of $593 per patient mainly by reducing ED visits and hospitalizations (Dewan, 2011). However, another VHA study of a comprehensive COPD care management program was prematurely stopped due to excess mortality in the intervention group (Fan, 2012).

Pulmonary rehabilitation is associated with reduced direct healthcare costs and an analysis of 592 pulmonary rehabilitation participants revealed an annual $344 (Canadian; approximately $291 US) per person decrease in overall healthcare costs (Golmohammadi, 2004). Hospital at home also reduces COPD related healthcare costs (Nicholson, 2001; Puig-Junoy, 2007; Steinel, 2003). A Spanish program found that among 180 patients presenting to the ED with a COPD exacerbation, home care by a specialized respiratory nurse reduced the average direct healthcare cost per patient by euro 810 (95% CI, euro 418–1,169) (approximately $955, US dollars) compared with hospitalization (Puig-Junoy, 2007). In-home healthcare by a pulmonary specialty team reduces hospitalizations, ED visits, and skilled nursing facility utilization, and decreases overall costs by $13,000 per patient annually (Steinel, 2003).

2.4 Conclusion

Epidemiology studies have demonstrated strong associations between tobacco smoke inhalation and the development of COPD. However, in the US and developed world, only 70–80% of individuals with COPD have a history of smoking. Other factors contributing to the development of COPD include indoor and outdoor air pollutants, workplace dust and fumes, childhood lower respiratory disorders including asthma, and pulmonary infections (tuberculosis and human immunodeficiency virus).

Although COPD prevalence is about 5–10% of the adult US population, these estimates may significantly underestimate COPD and up to three quarters of individuals
with evidence of airflow obstruction may not have a diagnosis. Further, clinical diagnosis of COPD based only upon respiratory symptoms is often incorrect.

The economic costs of COPD due to direct medical care and indirect effects due to work impairment or total disability are approaching $40 billion annually in the US and may reach $50 billion by 2020. Appropriate COPD management with medications and nonpharmacologic measures can reduce the cost of COPD.

### 2.5 Summary Points

1. Tobacco smoke inhalation is the major cause of COPD in the US but nearly one fifth of COPD cases are due to other exposures such as indoor and outdoor air pollutants, workplace dust and fumes, childhood lower respiratory disorders, and pulmonary infections.

2. COPD is under- and mis-diagnosed making accurate measurement of COPD prevalence difficult. Current estimates of COPD prevalence in the US are 5–10%.

3. COPD is a significant contributor to direct and indirect medical care and its cost is estimated to increase by nearly 50% by 2020.

### References


Epidemiology and Economic Consequences of COPD


3 COPD Recognition and Diagnosis: Approach to the Patient with Respiratory Symptoms

Key Points
1. Patients who present with respiratory symptoms such as cough, sputum production, wheezing, or breathlessness may have COPD, non-respiratory illnesses, or respiratory conditions other than COPD.
2. The initial evaluation of a patient who presents with respiratory symptoms includes a history, physical examination, spirometry testing, and a chest radiograph.
3. The diagnosis of COPD depends on the findings of appropriate symptoms in the right clinical context with airflow obstruction noted on spirometry testing.

3.1 Introduction

Patients who are seen in health care settings often present with respiratory symptoms including shortness of breath, cough, sputum production and chest discomfort or chest tightness. Although the focus of this primer is COPD, not every individual who has these respiratory symptoms and a history of smoking tobacco products has COPD. It is the task for the health care provider to be able to interview individuals who present with these symptoms and perform basic diagnostic tests to determine whether the cause for these symptoms is COPD or another respiratory or non-respiratory condition. This chapter will focus on the approach to a patient who presents with these respiratory symptoms. By obtaining the appropriate history and test results, the provider can determine the cause for the symptoms and, if it is COPD, initiate further management and treatment.

3.2 Patient Presenting with Respiratory Symptoms

An individual may present in a clinical setting with one of the following respiratory symptoms:
- Dyspnea or shortness of breath with activity or at rest
- Cough
- Sputum Production
- Chest Discomfort or Chest Tightness
- Wheezes or Rhonchi
### Table 3.1: Examples of Conditions other than COPD that may present with Respiratory Symptoms

<table>
<thead>
<tr>
<th>Condition</th>
<th>Non-respiratory</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac Disease</strong></td>
<td>Congestive Heart Failure</td>
</tr>
<tr>
<td></td>
<td>Valvular Heart Disease</td>
</tr>
<tr>
<td></td>
<td>Restrictive Cardiomyopathy</td>
</tr>
<tr>
<td><strong>Systemic Disease</strong></td>
<td>Collagen Vascular Disease</td>
</tr>
<tr>
<td><strong>Neuromuscular Disease</strong></td>
<td>Myasthenia Gravis</td>
</tr>
<tr>
<td></td>
<td>Amyotrophic Lateral Sclerosis</td>
</tr>
<tr>
<td></td>
<td>Multiple Sclerosis</td>
</tr>
<tr>
<td><strong>Infectious Disease</strong></td>
<td>Epstein Barr Virus infection leading to Chronic Fatigue Syndrome</td>
</tr>
<tr>
<td><strong>Hematologic Disease</strong></td>
<td>Myelodysplastic Syndrome</td>
</tr>
<tr>
<td></td>
<td>Lymphoma, leukemia or anemia</td>
</tr>
<tr>
<td><strong>Deconditioning</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Weight Gain/Obesity</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Adverse Reaction to Medication</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory Conditions other than COPD</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Airway Diseases</strong></td>
<td>Asthma</td>
</tr>
<tr>
<td></td>
<td>Bronchiectasis</td>
</tr>
<tr>
<td></td>
<td>Bronchiolitis Obliterans</td>
</tr>
<tr>
<td><strong>Interstitial Diseases</strong></td>
<td>Idiopathic Pulmonary Fibrosis</td>
</tr>
<tr>
<td></td>
<td>Non-specific Interstitial Pneumonitis</td>
</tr>
<tr>
<td></td>
<td>Sarcoidosis</td>
</tr>
<tr>
<td></td>
<td>Pneumoconiosis</td>
</tr>
<tr>
<td><strong>Other Respiratory Conditions</strong></td>
<td>Pulmonary Emboli</td>
</tr>
<tr>
<td></td>
<td>Pulmonary Hypertension</td>
</tr>
</tbody>
</table>

These symptoms are not specific to COPD or even to other respiratory illnesses and can be seen in other conditions that will require further investigation. Table 3.1 includes other conditions or causes of these respiratory symptoms other than COPD.
3.2.1 Further Discussion of Dyspnea/Shortness of Breath

Of the respiratory symptoms that individuals with COPD may have, dyspnea or breathlessness is a very common presenting symptom. Fifty percent of patients seen in acute care clinical settings present with the symptom of dyspnea (Parshall, 2012). The various descriptors of dyspnea can include: shortness of breath, air hunger, labored breathing, can’t get a deep breath, chest tightness, or heavy breathing. The American Thoracic Society’s definition of dyspnea is as follows: Dyspnea is a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity (Parshall, 2012). Like other symptoms that an individual may experience (pain, hunger, thirst, etc.), dyspnea is actually comprised of two separate but interacting elements: sensation and perception.

1. Sensation: the neural activation resulting from stimulation of peripheral neural receptors that varies based on the load, intensity and duration of the stimulation. Also, there are differences among the responses of different peripheral neural receptors.

2. Perception: the reaction of the individual to the neural activation that includes processing of that neural information along with other input including psychological, cultural, and behavioral factors.

In other words, dyspnea, like pain, is comprised of sensory and affective components. The sensory elements are the peripheral neural receptors as shown in Table 3.2.

In normal physiological states (e.g., exercise) and in disease states, stimulation of these peripheral receptors results in neural activation that is transmitted from the thorax to the central nervous system through pathways such as the vagus nerve and spinal cord afferents.

The neural traffic is then received in nuclei in the pons of the brainstem such as the nucleus of the tractus solitarius and in the medulla oblongata. From these locations, there are neural connections to the cortical sensory centers where this neural input is processed in the cortex along with other input depending on behavioral and cultural influences with the resulting sensation being noted as dyspnea or breathlessness. The latter processing is the affective component of the sensation of dyspnea.

Although an individual with disease may note breathlessness as a symptom of hypoxemia and hypercarbia, the input from chemoreceptors is only one signal that can cause the sense of dyspnea. In other scenarios, it is the input from other peripheral receptors that is noted as shortness of breath. As a result, for those individuals who do not exhibit hypoxemia but still note dyspnea, addition of supplemental oxygen will not relieve their dyspnea unless there is some placebo effect that is part of the behavioral input for the perception of dyspnea.

Dyspnea can be scored by different scales noted in Table 3.3. Dyspnea can be an alarming and distressing symptom for many individuals; it is influenced by both the sensory input from peripheral neural receptors; and it can be the result of disease
states in the lungs (airways and interstitium), the respiratory muscles, the chest wall, or the central vasculature.

As dyspnea is often distressing and anxiety-provoking and can lead to overall limitation in activities, the use of anxiolytics for patients with COPD is often a useful adjunctive therapy. Respiratory depression is a potential complication of the medications used to relieve anxiety (such as benzodiazepines).

For patients with COPD, the greater the impairment as determined by clinical scores such as the BODE Index (BMI, airflow obstruction, dyspnea and exercise capac-

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**Table 3.2: Sensory: Pulmonary Afferent Neural Receptors and other Afferent Neural Input**

<table>
<thead>
<tr>
<th>Sensory: Pulmonary Afferent Neural Receptors and other Afferent Neural Input</th>
<th></th>
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<tbody>
<tr>
<td>Airway Irritant Receptors</td>
<td></td>
</tr>
<tr>
<td>Within Lung Parenchyma/Interstitium</td>
<td></td>
</tr>
<tr>
<td>Slowly Adapting Stretch Receptors</td>
<td></td>
</tr>
<tr>
<td>Rapidly Adapting Stretch Receptors</td>
<td></td>
</tr>
<tr>
<td>C-Fibers (bronchial and pulmonary)</td>
<td></td>
</tr>
<tr>
<td>Respiratory Muscles/Chest Wall</td>
<td></td>
</tr>
<tr>
<td>Muscle spindles</td>
<td></td>
</tr>
<tr>
<td>Golgi tendon organs</td>
<td></td>
</tr>
<tr>
<td>Carotid Bodies, aortic bodies, central medullary chemoreceptors</td>
<td></td>
</tr>
<tr>
<td>Vascular receptors</td>
<td></td>
</tr>
<tr>
<td>Right Atrial and Left Atrial mechanoreceptors</td>
<td></td>
</tr>
<tr>
<td>Pulmonary Artery baroreceptors</td>
<td></td>
</tr>
<tr>
<td>Right Ventricular strain receptors</td>
<td></td>
</tr>
</tbody>
</table>

**Table 3.3: Scales for scoring Dyspnea**

<table>
<thead>
<tr>
<th>Scales for Scoring Dyspnea</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Questionnaires</td>
<td></td>
</tr>
<tr>
<td>Borg Score: 6 to 20</td>
<td></td>
</tr>
<tr>
<td>Visual Analog Scale (VAS): 100 mm</td>
<td></td>
</tr>
<tr>
<td>Oxygen Cost Diagram (OCD): 13 activities with increasing oxygen requirements</td>
<td></td>
</tr>
</tbody>
</table>
The presence of a respiratory symptom such as dyspnea does not necessarily indicate the disease process is in the lungs but could be in the heart, the circulation, the respiratory muscles or the chest wall. When a patient presents with respiratory symptoms such as dyspnea, the approach to determining the cause for these symptoms is described in Figure 3.1.
3.3.1 Exclude Causes of Symptoms other than Lung Disease

Based upon the initial presentation, relevant medical history and initial evaluation, it may be determined that the cause for the symptoms of dyspnea, chest discomfort, etc. is due to disease processes such as cardiac disease (see Table 3.1). For example, if the cause for these symptoms is cardiac, then the following would be useful: medical history especially relating to cardiac disease, diagnostic testing including electrocardiogram, echocardiogram, and stress testing. Once non-respiratory diseases are excluded or are not considered to be the prime reason for the current symptoms, then evaluation of respiratory causes can be initiated.

3.3.2 Respiratory Causes for Symptoms

The respiratory causes for symptoms of dyspnea, cough, sputum production, and chest tightness or discomfort can be divided into primarily airways diseases (such as COPD, asthma, bronchiectasis) or interstitial/parenchymal diseases (interstitial lung disease, pneumoconiosis, alveolar filling disease). Other possible respiratory diseases such as pulmonary vascular disease, pleural disease, or neuromuscular disease involving the respiratory muscles may also be considered.

3.3.2.1 Initial Evaluation of Respiratory Processes

The first steps for the evaluation of possible respiratory disease include history, physical examination, spirometry testing and chest radiograph.

**History:** Detailed respiratory, environmental and occupational history will need to be performed, including all personal habits such as smoking.

**Physical Examination:** focusing on the respiratory system for signs of respiratory insufficiency including use of accessory muscles, chest wall abnormalities, and auscultation for adventitial sounds.

**Spirometry Testing:** The technical details for the performance of spirometry testing will be discussed in greater detail in Chapter 4 of this primer. The interpretation of spirometry test results to help identify the type of respiratory condition will be discussed in greater detail in Chapter 4.

**Chest Radiograph:** A standard PA and lateral chest radiograph can be performed as part of the initial evaluation for any individual who presents with respiratory symptoms. It may not show any specific findings (not sensitive for some airways diseases or mild involvement with interstitial lung disease (ILD) or pulmonary vascular disease). However, there may be findings that will help identify certain patterns of disease presentations such as emphysematous changes in patients with COPD or interstitial markings in patients with ILD. Further description of the radiographic images for patients with COPD can be found in Chapter 5 of this COPD Primer.
3.3.2.2 Further Evaluation of Causes of Respiratory Symptoms after Spirometry Test Results

If the initial evaluation suggests that the patient’s respiratory symptoms are most likely due to a respiratory condition/disease, then the initial spirometry test results can provide information as to the type of impairment and in turn the type of disease that is being considered. Figure 3.2 is an algorithmic approach based on the results of the spirometry testing.

After excluding non-pulmonary causes of the symptoms and performing the initial screening tests including spirometry, the interpretation of spirometry can reveal normal results, airflow obstruction, or possible restriction (as mentioned, further explanation for the performance and interpretation of spirometry testing will be discussed in Chapter 4).

If airflow obstruction is found on the screening spirometry, possible conditions include COPD or asthma; other airways diseases could also present with airflow obstruction and asthma may present with a normal spirometry.
3.4 COPD

As the algorithm indicates, if the spirometry test results show airflow obstruction and the most likely disorder is COPD, then other clinical information and further diagnostic test results can help establish that COPD is present. Recent research indicates that COPD is not a single disease with a common pathogenesis but a syndrome composed of symptoms and findings in the presence of known risk factors.

3.4.1 Definition of COPD

As stated in the Key Points at the beginning of this chapter, the diagnosis of COPD depends on the findings of appropriate symptoms in the right clinical context with airflow obstruction noted on spirometry testing.

The following factors are considered when determining whether a patient has COPD:
- COPD is a syndrome related to the appropriate history, clinical signs and symptoms, physiologic and radiographic findings including the presence of airflow obstruction by spirometry (ATS, 2004).
- The airflow obstruction does not normalize or is not fully reversible.
- Various organizations define airflow obstruction differently. The American Thoracic Society/European Respiratory Society (ATS/ERS) definition uses the lower limit of normal (LLN) for the ratio of FEV$_1$/FVC based on reference equations, primarily NHANES III reference equations for spirometry (Hankinson, 1999) whereas the Global Initiative for chronic Obstructive Lung Disease (GOLD, 2013) criterion uses a fixed cutoff of 70% for the ratio of FEV$_1$/FVC. In either case, airflow obstruction is considered to be a reduced FEV$_1$/FVC ratio (either below LLN or 70%). However, just like the syndrome of COPD is a continuum from no disease to severe disease, the presence of airflow obstruction itself can be a continuum from no airflow obstruction to very severe airflow obstruction. There are instances with borderline airflow obstruction with values of FEV$_1$/FVC above the threshold value (whether it is the LLN or 70%) that still may have some likelihood of abnormality of airways disease that would be consistent with a clinical diagnosis of COPD. For these borderline cases, the use of reduced mid-expiratory flow values would be helpful to identify instances where there would be intermediate probability or likelihood of airflow obstruction that would be consistent with COPD. The mid-expiratory flow ratio (MEFR) can be useful in these circumstances. When this ratio (actual FEF$_{25-75}$/actual FVC)/(predicted FEF$_{25-75}$/predicted FVC) is < 0.70, at a time when the FEV$_1$/FVC ratio is above the lower cutoff for airflow obstruction, there is an intermediate probability that there is airflow obstruction that would be consistent with COPD.
- Clinical manifestations of COPD and asthma can overlap.
Historically, COPD was considered to be composed of two disorders: chronic bronchitis and emphysema. More recent information suggest that as a syndrome, COPD is a heterogeneous disorder that is actually composed of several phenotypes. (See further discussion of COPD phenotypes in Chapter 5 on Radiology).

The history that is usually associated with the development of COPD is related to tobacco smoking with or without environmental or occupational risk factors. There may also be genetic predisposition or susceptibility for the development of COPD combined with exposure to personal or environmental/occupational risk factors.

The deficiency of the enzyme α-1 antitrypsin is seen in about 1% of patients with COPD.

When COPD is considered a syndrome, there may be a different approach to establish the presence or diagnosis of COPD. As with other clinical conditions or disorders (e.g., pulmonary embolus, obstructive sleep apnea), there may be a degree of certainty or likelihood for the establishment of the diagnosis that in turn is dependent on physiological, historical, and clinical factors. Stated differently, we use Bayes Theorem for the determination of the likelihood for the presence of a disorder that is dependent upon the context or the pre-test probability of the disorder or condition.

The factors used for the diagnosis of COPD are:

1. Physiological:
   - Presence of airflow obstruction defined primarily by a reduced FEV₁/FVC but may include other spirometric parameters as well (e.g., reduced mid-expiratory flow rates).
   - Other physiological factors as described below that may be confirmatory for the presence of COPD (e.g., air-trapping, hyperinflation, increased airways resistance, reduced diffusing capacity).

2. Historical:
   - Smoking history that is considered substantive (e.g., greater than 20–40 pk-ys).
   - Previous clinical diagnosis of COPD by a health care provider.
   - Other environmental or occupational exposures that are associated with the development of airways diseases.

3. Clinical:
   - Appropriate respiratory symptoms: dyspnea, cough, sputum production, chest tightness, wheezing.
   - Other clinical diagnostic testing: CT scans or chest radiographs showing emphysematous changes.
   - Use of medications for airways diseases including inhaled bronchodilators, inhaled and/or oral corticosteroids.
The weighting of these factors for the determination of the likelihood of COPD is not entirely clear but some of these factors are probably more significant than others (airflow obstruction, smoking history, previous diagnosis of COPD, presence of respiratory symptoms). See Figure 3.3 for illustration of this approach to the diagnosis of COPD.

The weighting of these factors for the determination of the likelihood of COPD is not entirely clear but some of these factors are probably more significant than others (airflow obstruction, smoking history, previous diagnosis of COPD, presence of respiratory symptoms). See Figure 3.3 for illustration of this approach to the diagnosis of COPD.

### 3.4.2 Other Diagnostic Tests to Help Confirm the Presence of COPD

As mentioned above, there are other physiological test results that support the diagnosis of COPD. These confirmatory diagnostic tests include more complete pulmonary function testing such as measurement of lung volumes by body plethysmography or nitrogen washout testing. In some patients with COPD, the lung volume measurements show hyperinflation (a total lung capacity that is greater than the upper limits of normal for that parameter) or air-trapping (a residual volume values that is greater than the upper limits of normal for that parameter).
Diffusing capacity measurement could also be performed. Diffusing capacity values give an indication of the lungs ability to take up oxygen (using carbon monoxide as the surrogate gas for oxygen). Patients with COPD who have emphysematous changes may have a reduced diffusing capacity since there is a loss of pulmonary capillary surface area.

As will be discussed in Chapter 5, radiographic imaging beyond chest radiographs can be useful for patients with COPD. A CT scan of the chest is a more sensitive approach to identify the presence of emphysematous changes as well as any interstitial changes that may be present that are not obvious by a standard chest radiograph.

Cardiopulmonary exercise testing may also be useful for the determination of exercise performance for these patients and, if there is limitation to exercise performance, whether the cause of the limitation is due to COPD (Eschenbacher, 1990).

If the confirmatory tests indicate that the disease process is COPD, then the severity of the disease and recommendations for management can be found in other chapters in this COPD Primer (e.g. Chapter 14).

### 3.5 Asthma

If airflow obstruction is interpreted from the screening spirometry and the disease is thought to be asthma instead of COPD, then confirmatory testing can also be done. Although there may be clinical overlap between these two obstructive airways diseases, there can be differences that help distinguish one condition from the other as shown in Table 3.4.

#### Table 3.4: Distinguishing Asthma and COPD

<table>
<thead>
<tr>
<th></th>
<th>Asthma</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predominant Inflammatory Cells</td>
<td>Eosinophils</td>
<td>Neutrophils</td>
</tr>
<tr>
<td>Cytokines</td>
<td>Th2: IL-4,5,9,13</td>
<td>Th1: IFN-γ</td>
</tr>
<tr>
<td>Air Flow Limitation</td>
<td>Can normalize</td>
<td>Does not normalize</td>
</tr>
<tr>
<td>Age of onset</td>
<td>Younger</td>
<td>Older</td>
</tr>
<tr>
<td>Atopy/allergies</td>
<td>More likely</td>
<td>Less likely</td>
</tr>
<tr>
<td>Variability</td>
<td>Varies day-to-day</td>
<td>Less likely to vary</td>
</tr>
<tr>
<td>Medication</td>
<td>Inhaled corticosteroid initially</td>
<td>Inhaled corticosteroid after bronchodilators are used</td>
</tr>
</tbody>
</table>
For asthma, the inflammatory component found in the airways can be eosinophilic or neutrophilic but for COPD, it is usually neutrophilic. Other aspects of the inflammation found in asthma include T-helper type-2 lymphocytes with mediators that can include IL-4, 5, 9 and 13. For COPD, the inflammation may be more of T-helper type-1 lymphocytes with Interferon-γ (IFN-γ). The airflow obstruction with asthma can return to within normal limits at baseline or as a result of medication but this normalization usually does not occur with COPD. Asthma is clinically seen as developing in younger individuals who have an allergic component to their disease. There is usually more day-to-day variability in asthma as a result of exposure to different triggering agents such as environmental antigens. Finally, the management of these two airways diseases differs: inhaled corticosteroids are used as the primary controller medication for asthma and bronchodilators such as long-acting anticholinergic agents are more useful in COPD.

Confirmatory tests to identify asthma include standard lung function tests such as lung volume measurements and diffusing capacity and bronchoprovocation challenge test such as methacholine testing. The usefulness of such a bronchoprovocation challenge test for asthma was described in the NHLBI Guidelines for the Diagnosis and Management of Asthma EPR-3:

“Bronchoprovocation with methacholine, histamine, cold air or exercise challenge may be useful when asthma is suspected and spirometry is normal or near normal. A positive test is diagnostic for the presence of airway hyperresponsiveness, a feature of asthma but can be present in other conditions. A positive test is consistent with asthma; a negative test may be more helpful to rule out asthma” (NHLBI, 2007).

In patients with asthma, lung volume measurements may reveal hyperinflation and air-trapping but may also be within normal limits. For diffusing capacity measurements in asthma, the values can be normal or even elevated as compared to many patients with COPD where the diffusing capacity measurement is reduced (especially if emphysema is present).

### 3.6 Interstitial Lung Disease

If the screening spirometry for individuals who present with respiratory symptoms (including dyspnea and cough) reveals a possible restrictive impairment pattern instead of airflow obstruction and the chest radiograph shows interstitial markings, then the disease process could be an interstitial lung disease. Confirmatory testing to help establish the diagnosis of an interstitial lung disease includes further lung function testing with lung volume measurement and diffusing capacity. Lung volume values would be expected to confirm the presence of a restrictive lung defect that had been suggested by spirometry. Both total lung capacity and residual volume results might be below their respective lower limits of normal (LLN). Diffusing capacity measurement may also be reduced as the interstitial disease process has reduced
the pulmonary capillary surface area and reduced the ability of the lungs to take up oxygen.

CT scans of the chest, especially high-resolution CT scans, are useful in the diagnosis of interstitial lung diseases by showing specific patterns that may be associated with certain ILD classifications (Webb, 2009).

Cardiopulmonary exercise testing may reveal pulmonary or ventilatory limitation as well as possible pulmonary vascular limitation. The latter may be seen if there is associated pulmonary hypertension as a result of reduced pulmonary vascular compliance due to the interstitial disease process involving the pulmonary vasculature.

Finally, in some instances, a lung biopsy may be needed. This histopathologic diagnosis would not only help establish the specific type of ILD but may also be useful for prognosis and for disease management.

3.7 Summary Points

1. Patients who present with respiratory symptoms require a standardized approach to determine the cause for their symptoms.
2. Not all patients who experience respiratory symptoms and have a significant smoking history have COPD.
3. Other conditions that could explain the presence of symptoms of dyspnea, cough, and chest discomfort include other respiratory diseases (airways diseases such as asthma and bronchiectasis; or restrictive lung diseases including interstitial lung diseases) and non-pulmonary processes such as heart failure.
4. History, physical examination, chest radiograph and spirometry are part of the initial screening evaluation needed to help determine the type of disease process but more advanced testing may be needed subsequently.

References


4 Pulmonary Function Testing: Spirometry: Presence and Severity of Airflow Limitation/Obstruction

Key Points
1. Spirometry is used to detect airflow limitation which is a key component for the diagnosis of COPD.
2. Spirometry testing must be done correctly to obtain acceptable and repeatable results.
3. Airflow limitation is present when the ratio of the post-bronchodilator forced expiratory volume in one second divided by the forced vital capacity (FEV₁/FVC) is less than the lower limit of normal or < 0.70.

4.1 Introduction

COPD is characterized by airflow limitation that does not normalize after the use of a bronchodilator. Spirometry is the diagnostic test that is used to confirm the presence of airflow limitation. However, the clinical diagnosis of COPD requires more than the establishment of spirometry-determined airflow limitation. There should also be the presence of appropriate symptoms and known risk factors. As discussed in Chapter 3 on the recognition and diagnosis of COPD, this condition is more of a syndrome than a disease, with the diagnosis depending on the findings of appropriate symptoms in the right clinical context with airflow obstruction noted on spirometry testing. Once a screening questionnaire has identified an individual who may have COPD (by symptoms and history), spirometry is then performed. See Figure 4.1 for an example of a patient undergoing spirometry testing.

Spirometry is a test of respiratory function that measures the volume of air that an individual can inhale and exhale, usually in a forceful manner. After the individual fills his or her lungs to maximal capacity, he or she is asked to exhale forcefully while the exhaled volume is measured over time until the expiration is complete. When graphed, this volume–time relationship is known as a spirogram. The device used for the measurement is a spirometer. The important parameters determined by this test include:
- the total volume that is exhaled forcefully; the forced vital capacity (FVC);
- the volume of air that is exhaled in the first second of time; the forced expiratory volume in 1 second (FEV₁);
- the ratio between these two values: FEV₁/FVC.

Spirometry is useful in the evaluation of a patient who presents with respiratory symptoms (e.g., dyspnea, cough, sputum production, chest tightness, and wheezing).
Thus, the results of spirometry can be interpreted according to specific patterns of normality or abnormality, including airflow obstruction, possible lung restriction, or a mixed pattern of obstruction and possible restriction. If the spirometry test results are interpreted as abnormal, the individual may then be referred for more complete pulmonary function testing and further evaluation.

### 4.2 Reasons for Spirometry Testing

Reasons for performing spirometry in a clinical setting include:
- Evaluate dyspnea or shortness of breath in an individual
- Determine the presence and type and severity of pulmonary impairment or limitation
- Pre-operative assessment to determine the respiratory risk of a patient being considered for surgery
- Detect if there are changes in lung function over time that may indicate development or worsening of a pulmonary disease
- Determine the benefits or worsening effects of treatment
- Identification of a patient with chronic obstructive pulmonary disease or COPD

It is this last reason that is the focus of this chapter and this primer.

### 4.3 Spirometry Screening for COPD

Although it has been previously suggested that spirometry should be performed in any individual over 45 years of age who is a smoker for the identification of patients with COPD (Ferguson, 2000), the U.S. Preventive Services Task Force in March of 2008 released a recommendation that spirometry was not indicated as a screening test for COPD unless the individual presented with respiratory symptoms including chronic cough, increased sputum production, wheezing or dyspnea (USPSTF, 2008). More recently, the US Preventive Services Task Force is re-examining its position for spirometry screening for COPD asking the question whether screening asymptomatic adults age 40 years and older for COPD could improve health-related quality of life or reduce morbidity or mortality (USPSTF, 2014). However, there may also be selected populations such as U.S. Veterans who have a high rate of smoking and both an increased prevalence of COPD as well as undiagnosed COPD (Murphy, 2013). It is in this population that efforts are being focused to use a specifically designed questionnaire (Sogbetun, 2014) followed by spirometry to screen for airflow obstruction and COPD.

### 4.4 Limitations of Spirometry

Although spirometry can provide useful diagnostic and screening information, it has a few limitations. As a screening test, the results of spirometry can show normal results or restrictive or obstructive disease patterns, but the results cannot identify a specific disease. For example, a person’s spirogram may show a low FEV₁, but a physician may not be able to determine whether the cause is from asthma, emphysema, or some other obstructive or restrictive lung disease. Additional information, including health and exposures histories, physical examination, chest imaging, and other pulmonary function testing such as lung volumes and diffusing capacity may be needed to make a diagnosis.

Spirometry often can detect obstructive diseases in its early stages, but for some of the restrictive diseases, it may not be sensitive enough to show abnormalities before extensive, and in some cases, irreversible damage has been done. For example, presence of interstitial markings may be found on chest radiographs or CT scans of the chest while spirometry results are still within normal limits.
Three Phases of a Spirometry Test

The actual performance of a spirometry test is made up of three separate but critical phases:

1. The subject must take in as deep of breath as possible filling his or her lungs to total lung capacity
2. Then without hesitation, the subject must blast out or exhale the air forcefully
3. The subject should then continue to exhale until told to stop or unable to continue

See Figure 4.2 for an image showing the three phases of a spirometry test.

As will be discussed later, the performance of spirometry must meet certain criteria of acceptability and repeatability that depend on the ability of the subject to perform successfully each of these three phases of the test.
4.6 Displaying the Results of Spirometry Testing

When a spirometry test is performed, the technician coaches the subject or patient to take in a deep inspiration to completely fill their lungs and then without hesitation to exhale forcefully into the spirometer. The resulting exhaled volume of air and the flow rate of the exhaled air are measured and plotted on two different graphs (see Figure 4.3 and 4.4 for one form of the display of spirometry testing: volume of exhaled air against the time of exhalation).
Three spirometric measurements are particularly useful: **forced vital capacity (FVC)**, **forced expiratory volume at one second (FEV₁)**, and the **ratio of the FEV₁ to the FVC (FEV₁/FVC)**. Computerized spirometers frequently print out six or more measures of flow or volume. However, for most purposes, the FVC and FEV₁ suffice. The FVC is the total volume of air exhaled after a ** Forced Expiratory Maneuver** (the act of exhaling as hard and fast as possible after maximal inspiration). The FEV₁ is the amount of air that a person breathes out during the first second of a forced expiratory maneuver.

Figure 4.5 is a different presentation of the data obtained with spirometry: the display of the flow rate of exhaled and inhaled air against the volume of air exhaled. This type of graphical representation (flow-volume curve) is quite useful in assessing the quality of spirometry testing especially for the first second of exhalation. The different colored lines refer to the baseline measurement of spirometry (red line) and repeat spirometry after the administration of a bronchodilator (blue line). Also, the

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**Figure 4.5: Flow-Volume Loop.** In this type of graph, the flow rate of air in liters per second that is exhaled (or inhaled) is plotted against the volume of air in liters that is exhaled (or inhaled).
dots refer to the predicted values for flow rates for this individual. The volume-time graphs are also shown in this figure for pre- and post-bronchodilator spirometry. The FVC is the greatest point of the curve on the x-axis (in this example, it is 4.7 liters). However, the FEV₁ is not obvious since the time of exhalation is not shown. Instead, the spirometer has marked the location of the FEV₁ by a vertical line on the exhalation limb of the flow volume loop (in this example, the FEV₁ is 3.9 liters).

Spirometry test results can include many more parameters of exhaled flow including the peak expiratory flow rate (FEFmax) and mid-expiratory flow rates (FEF25–75%) as well as other instantaneous flow rates (FEF50%). However, for practical and clinical purposes, the three parameters mentioned below are the most important:

- Forced Vital Capacity (FVC) expressed in liters
- Forced Expiratory Volume in One Second (FEV₁) also expressed in liters
- The ratio of FEV₁/FVC expressed in percentage (%)

### 4.7 Acceptability and Repeatability Criteria of Spirometry Testing

Spirometry testing must be done in a high quality manner to obtain accurate information about the lung health of each patient. To ensure that the test results provide us with truly representative information, each forced maneuver must be examined for acceptability and each test session must be examined for repeatability. These criteria of acceptability and repeatability are described in detail in the American Thoracic Society/European Respiratory Society (ATS/ERS) recommended guidelines for spirometry testing (Miller, 2005). Spirogram results are used to detect possible conditions that affect the subject’s ability to exhale as fully and forcefully as possible. The results are compared either to the subject’s previous spirogram results if they are available or to established reference or predicted results that would be expected for a person with his/her characteristics (e.g., sex, age, height, etc.). If inaccurate results are obtained, the information from the comparisons will not be correct, creating the potential for not detecting serious lung diseases, or, diagnosing disease where none exists. Therefore, the goal of each testing session is to obtain acceptable maneuvers and a repeatable test session. That said, patients with lung disease may have a harder time producing acceptable and repeatable results. Acceptable tests are free from artifacts such as cough or glottis closure during the first second of exhalation, early termination (exhalation should be at least 6 seconds), variable effort, leak, or obstruction of the mouthpiece (Miller, 2005). There should be a quick start to the exhalation with the back extrapolated volume <5% of the FVC or 0.150 liters, whichever is greater. After three acceptable maneuvers the maximal two FEV₁’s and FVC’s should be within 150 ml of each other for the results to be repeatable (Miller, 2005). No more than 8 maneuvers should be attempted due to patient fatigue.
4.8 Measurements from Spirometry Testing

Once testing is completed, the spirometry test results for that individual (specifically the forced expiratory volume in one-second (FEV$_1$), forced vital capacity (FVC) and the ratio of those two values FEV$_1$/FVC) are compared to predicted values based on established reference equations e.g. the third National Health and Nutrition Examination Survey (NHANES III) reference equations for spirometry (Hankinson, 1999).

4.9 Patterns of Spirometry Impairment or Limitation

In addition to a normal pattern of spirometry test results, different impairments produce distinct spirometry patterns:

- Obstructive Defect Pattern or Airflow Limitation or Obstruction
- Restrictive Lung Defect Pattern
- Mixed Impairment with both Airflow Obstruction/Limitation and Lung Restriction.

4.9.1 Airflow Obstruction Pattern

In this pattern, the rate of airflow is reduced due to either narrowing of the airways in the lung (as in asthma or chronic bronchitis) or loss of elastic recoil (as in emphysema) reducing the rate of exhaled airflow. See Figure 4.6 and 4.7 for volume time displays of the airflow obstruction pattern.

With airflow obstruction, there is a reduction in the amount of air that is exhaled in the first second (FEV$_1$) as well a reduction in the ratio of FEV$_1$ to FVC. In fact, it is the reduced ratio of FEV$_1$ to FVC or FEV$_1$/FVC % that is the hallmark of airflow obstruction. In this example, the normal spirometry results show a FEV$_1$ of 3.0 liters and a FVC of 4.0 liters; therefore, the ratio of FEV$_1$/FVC is 3.0/4.0 or 75%. For the spirometry showing airflow obstruction or limitation, the FEV$_1$ is 1.0 liters, the FVC is 3.7 liters, and the ratio of FEV$_1$/FVC is 1.0/3.7 or 27%.

See Figure 4.8 for an example of moderately severe airflow obstruction with a flow-volume display. At baseline, the FVC is 2.8 liters, the FEV$_1$ (by the vertical mark) is 1.3 liters, and the ratio of FEV$_1$/FVC is 1.3/2.8 or 46%. After the bronchodilator, the FVC is now 3.7 liters, the FEV$_1$ is 1.9 liters and the FEV$_1$/FVC is 1.9/3.7 or 51%.

Figure 4.9 is an example of severe airflow obstruction with a flow-volume display.

Examples of lung diseases with airflow obstruction are COPD including chronic bronchitis and emphysema, asthma, bronchiectasis, and bronchiolitis obliterans.
**Figure 4.6:** Volume-time graph of Airflow Obstruction. In this case, as compared to a normal pattern of exhaled volume of air, there is a decreased volume of exhaled air in the first second of exhalation.

**Figure 4.7:** Volume-time graph of airflow obstruction showing measurements of FEV₁ and FVC and the ratio of FEV₁ to FVC (FEV₁/FVC)
4.9.2 Restrictive Lung Defect Pattern

In the case of a restrictive lung defect pattern, the total amount of exhaled air is reduced. This means the Vital Capacity or FVC is reduced. See Figure 4.10 and 4.11 as examples of volume-time displays of a restrictive lung defect.

In a restrictive lung defect, the rate of emptying of the air from the lung may not be reduced so the relationship between FEV\textsubscript{1} and FVC is normal. That said, because the FVC is reduced, the FEV\textsubscript{1} will be reduced proportionally with the FEV\textsubscript{1}/FVC ratio being maintained and not reduced or, even on occasions, increased. In this particular case, the FVC is reduced as is the FEV\textsubscript{1} but the ratio of FEV\textsubscript{1}/FVC is maintained or even increased compared to normal. For a restrictive lung defect, the hallmark is the reduced FVC. In this example, the normal spirometry results show an FEV\textsubscript{1} of 3.0 liters and FVC of 4.0 liters for a ratio of FEV\textsubscript{1}/FVC of 3.0/4.0 or 75%. For the spirometry showing restriction, the FEV\textsubscript{1} is 1.8 liters, the FVC is 2.2 liters and the ratio of FEV\textsubscript{1}/FVC is 1.8/2.2 or 82%.

See Figure 4.12 and 4.13 as examples of flow-volume displays of restrictive lung disease.

Since spirometry cannot measure the residual volume and, in turn, cannot determine the total lung capacity, spirometry can only suggest the presence of an actual restrictive lung defect. Further testing with lung volume measurements would be needed to confirm the presence of restriction.

Examples of lung diseases that can have a restrictive lung defect include interstitial fibrosis, hypersensitivity pneumonitis, pleural disease, chest wall deformities, pulmonary edema, and obesity.

4.9.3 Mixed Impairment with both Airflow Obstruction and Lung Restriction

Mixed impairment may be seen with combined lung diseases: a patient with a long smoking history who has COPD as well as the development of severe obesity leading to a restrictive lung defect. See Figure 4.14, 4.15 and 4.16 as examples of a volume time tracing and flow-volume displays for a mixed impairment result.

4.10 Interpretation of Spirometry Results

4.10.1 Reference Equations

There have been many studies published in the medical literature which have determined spirometry reference values from groups of relatively healthy persons. At this time, the American Thoracic Society (ATS) recommends using the reference values based on the third National Health and Nutrition Examination Survey (NHANES III) (Hankinson, 1999).
Figure 4.8: Flow-volume loop of Moderate Severity Airflow Obstruction. As can be seen in this graphical representation, the flow rate of air during exhalation is reduced throughout exhalation. This gives increased curvature or a greater concave shape to the expiratory limb of the flow volume loop which is another hallmark of airflow obstruction. Again, the different colored lines refer to pre-bronchodilator or baseline spirometry testing (red line) and post-bronchodilator testing (blue line).

Figure 4.9: Flow-volume loop of Severe Airflow Obstruction In this example, there is more severe airflow obstruction which can be seen by even more severely decreased expiratory flow rates. At baseline, the FVC is 2.7 liters and the FEV₁ is 0.4 liters for a ratio for FEV₁/FVC of 15%. After the bronchodilator, the FVC is 3.1 liters and the FEV₁ is 0.6 liters for a ratio for FEV₁/FVC of 19%.
Figure 4.10: Volume-time graph of Restrictive Lung Defect Pattern. In the case of a restrictive lung defect pattern, the total amount of air exhaled is reduced. This means the Vital Capacity or FVC is reduced.

Figure 4.11: Volume-time graph of Restrictive Lung Defect showing measurements of FEV₁ and FVC and the ratio of FEV₁ to FVC (FEV₁/FVC).
Figure 4.12: Flow-volume loop of a Restrictive Lung Defect. In a restrictive lung defect, the flow rates are maintained but the vital capacity (FVC) is reduced. This gives the appearance of a more vertical or upright flow-volume loop. In this case at baseline, the FVC is 3.2 liters and the FEV₁ is 2.9 liters for a ratio of FEV₁/FVC of 91%. There is really not much change after the use of a bronchodilator.

Figure 4.13: Another example of a Flow-volume loop for a Restrictive Lung Defect. Again note the more vertical appearance of the flow-volume loop in contrast to the horizontal appearance of the flow-volume loop for the patient with severe airflow obstruction. At baseline, the FVC is 3.2 liters and the FEV₁ is 2.7 liters for a ratio of FEV₁/FVC of 84%.
4.10.2 Racial Differences in Reference Equations

The NHANES III study provides a separate set of spirometry reference equations for men and women of African-American, Caucasian, and Mexican-American ethnic groups. The NHANES III study did not provide spirometry reference equations for Asian-Americans, American Indians, East Indians, or other ethnic groups. Other investigations suggest that spirometry results are not substantially different for American
Indians when compared to Caucasians living in the United States; therefore, NIOSH recommends that when testing American Indian patients, the reference equations for Caucasians be used. For Asian-Americans, until separate reference equations are published and accepted for Asian-American and East Indian ethnic groups, the NHANES III reference equations for Caucasians should be used, but a correction factor of 0.88 should then be applied to the predicted values for FVC and FEV₁ (Redlich, 2014).

### 4.10.3 The Lower Limit of the Normal (LLN) Range

The predicted value calculated from spirometry reference equations is the average or mean value observed from many healthy persons of the same age, gender, height, and race as the patient being tested. The predicted value is actually in the middle of a rather wide, bell-shaped distribution (range) of normal values. For instance, some healthy persons may have FVC values as much as 20% lower than the predicted value. The lower limit of the normal range (LLN) is the threshold below which a value is considered abnormal - usually the value is set so that 95% of a “normal” population will have values above the LLN value and, correspondingly, 5% of a “normal” population will have values below the LLN. The LLN is about 80% of the predicted value for FEV₁ and for FVC, but about 90% of the predicted value for the FEV₁/FVC ratio, and about 60% of the predicted value for the FEF₂₅–₇₅%. However, these are only rough “rules of thumb” and the exact LLN should be determined using the reference equations.
4.10.4 **What is Considered to Be Abnormal?**

Abnormalities detected by spirometry may show one of three patterns: obstructive, restrictive, or mixed impairment (both obstructive and restrictive). Patients with obstructive lung diseases, such as emphysema or chronic asthma, often have an abnormally low FEV<sub>1</sub>/FVC and a low FEV<sub>1</sub> (below the LLN). Patients with fibrotic lung diseases, such as asbestosis, often have an abnormally low FVC, but their FEV<sub>1</sub>/FVC will generally be above the LLN. Persons exposed to certain dusts, such as silica or coal mine dust, can develop either pattern of abnormality, or a mixed pattern with reductions of both the FEV<sub>1</sub>/FVC ratio and the FVC below the LLN. Occasionally, spirometry results from a patient without any apparent health problems are found to be slightly below the LLN. In contrast, it is not unusual to have high FVC or high FEV<sub>1</sub> spirometry values. Young adults who were competitive athletes in high school, trade school, or college (while their lungs were still growing) may have a percent predicted FVC above 120%.

4.10.5 **Determine Predicted Values and % of Predicted Values**

Spirometry reference or predicted values, percent predicted values, and the LLN’s for an individual can be reported from the automated spirometry system that has already been programmed with the appropriate reference equations. The percent of predicted values refers to the actual measured value of the spirometric parameter (e.g., FEV<sub>1</sub> or FVC) divided by the predicted or reference value for that individual times 100 for %, or:

\[
\text{%Pred FEV}_1 = 100.0 \times \frac{\text{Observed FEV}_1}{\text{Predicted FEV}_1}
\]

4.10.6 **Interpretation of Spirometry Test Results for Impairment Patterns**

As mentioned above, lower limits of normal (LLN) for the spirometric parameters are used to determine whether the results are normal or abnormal. The primary impairment patterns of airflow obstruction, a restrictive lung defect and mixed impairment are then determined by interpretation using these LLNs.

4.10.7 **Airflow Obstruction**

The criterion for the interpretation of the presence of airflow obstruction is the finding of a reduced FEV<sub>1</sub>/FVC or the numerical value of FEV<sub>1</sub>/FVC below the LLN for that
value. Some providers may decide to use the guidelines from the Global initiative for Chronic Obstructive Lung Disease: GOLD criteria for airflow obstruction (GOLD, 2013), when interpreting the results of spirometry. Those guidelines define an absolute cutoff for FEV1/FVC of 70% to determine the presence of airflow obstruction. The American Thoracic Society and European Respiratory Society recommend using the LLN from the reference equations chosen for the interpretation of spirometry test results (Pelligrino, 2005), (see “Controversy for Determination of Airflow Limitation/Obstruction” below).

The primary determinant of airflow obstruction is the FEV1/FVC ratio measured by spirometry: If FEV1/FVC < LLN, then airflow obstruction is present.

Once airflow limitation is determined to be present, the severity of limitation is then assessed based upon the FEV1 % of predicted value. Using the ATS/ERS guidelines for Interpretative Strategies for Lung Function Tests (Pelligrino, 2005), the following severity categories are used:

- Mild obstruction: FEV1 % predicted > 70% (which means the actual value measured is greater than 70% of the predicted value which in turn is based on the patient’s age, height and gender with correction for race as appropriate).
- Moderate obstruction: FEV1 % predicted <69% but > 60%
- Moderately severe obstruction: FEV1 % predicted <59% but > 50%
- Severe obstruction: FEV1 % predicted <49% but > 35%
- Very severe obstruction: FEV1 % predicted <34%

There may be patients whose results from spirometry testing or from complete pulmonary function testing (if available) may be equivocal for the presence of airflow limitation or COPD. As discussed in Chapter 3 on the Recognition and Diagnosis of COPD, just as the syndrome of COPD may range from no evidence of airways disease to severe COPD, the presence of airflow obstruction is also a continuum from no airflow obstruction to very severe airflow obstruction. In the case of possible borderline airflow obstruction when the FEV1/FVC is above the LLN, the use of reduced mid-expiratory flow rates adjusted for the FVC (the mid-expiratory flow ratio or MEFR) may be helpful (see Chapter 3).

4.10.7.1 Possible Restrictive Lung Defect
Because spirometry cannot measure residual volume (RV) and in turn total lung capacity (TLC), the test cannot determine the presence of an actual restrictive lung defect where the total lung capacity is reduced below its LLN. Instead if the FVC is reduced below its LLN, then the presence of a restrictive lung defect can be suggested. However, it should be stated that further testing including the use of lung volumes will be needed to confirm the presence of an actual restrictive lung defect.
If only spirometry results are available, then the presence of restriction would be suggested if the FVC is < LLN (especially if the FEV$_1$/FVC ratio is > LLN); however the comment should be made that lung volumes would be recommended for confirmation of the presence of a restrictive lung defect.

4.10.7.2 Mixed Impairment Pattern

It is possible that there might be both the presence of airflow obstruction and the presence of a possible restrictive lung defect. In that case, a mixed impairment pattern may be interpreted.

- Mixed impairment will be interpreted if there is both the presence of airflow obstruction and the suggestion of a restrictive lung defect.

4.10.7.3 Controversy for Determination of Airflow Limitation/Obstruction

As mentioned previously, the determination of the presence of airflow limitation or obstruction is in most cases the finding of a reduced FEV$_1$/FVC ratio. The controversy has been deciding below what value the FEV$_1$/FVC is considered to be reduced. The definition of airflow limitation or airflow obstruction has been a point of discussion based upon different statements from professional groups. Clinical guidelines for COPD disease management include the Global Initiative for Chronic Obstructive Lung Disease (GOLD, 2013), the VA/DoD Clinical Practice Guideline for Management of Outpatient Chronic Obstructive Pulmonary Disease (VA/DoD, 2007), and the American Thoracic Society/European Respiratory Society Standards for the Diagnosis and Management of Patients with COPD (ATS, 2004). These three guidance documents have recommended being more inclusive for identifying individuals who may have COPD and have proposed that the presence of airflow limitation exists when the post-bronchodilator FEV$_1$/FVC ratio is < 0.70. These guidelines acknowledge that this approach may be overly sensitive and include older individuals who are normal but who have an FEV$_1$/FVC ratio that is < 0.70. Other guidance documents are based on a statistical approach for the interpretation of airflow limitation using reference equations which in turn are based on population studies. The ATS/ERS document on Interpretative Strategies for Lung Function Tests states that the presence of an obstructive ventilatory defect exists when the FEV$_1$/FVC ratio is below the 5$^{th}$ percentile of its predicted value, a value referred to as the lower limit of normal or LLN for that ratio based on the chosen reference values (Pelligrino, 2005). The most recent revised GOLD guidance (GOLD, 2013) acknowledges that the LLN values are based on a normal distribution and that the use of a fixed ratio of 0.70 will result in more frequent diagnosis of COPD in the elderly.

These different thresholds for the definition of airflow limitation or obstruction, a fixed cutoff of 70% for the ratio of FEV$_1$/FVC or the LLN for this ratio, can yield very different diagnoses as is illustrated in Figure 4.17. As we age, the normal values
for FEV₁/FVC decrease and, in turn, the values for the LLN for the ratio of FEV₁/FVC also decrease. The regression line for the decline in the LLN for the FEV₁/FVC ratio with increasing age based upon the NHANES III reference equation is shown in this figure. As a result, younger individuals with an FEV₁/FVC above 70% but below the LLN would be classified as no airflow obstruction by use of a 70% cutoff but would be interpreted as airflow obstruction by use of the LLN (false negatives). On the other hand, older individuals with FEV₁/FVC ratios below 70% but above the LLN would be classified as having airflow obstruction by the use of a 70% cutoff but would have no airflow obstruction by use of the LLN (false positives).

**4.10.7.4 Bronchodilator Response**

There are times when clinicians want to assess a patient’s spirometric response to the one-time use of a bronchodilator. In those instances, the % change and absolute change in volume of FEV₁ and FVC is determined comparing the post-bronchodilator spirometry results to the baseline or pre-bronchodilator results.

- A significant response to the one-time use of a bronchodilator is a 12% increase in FEV₁ or in FVC with at least a 200 ml increase in that measurement.

There needs to be both the 12% increase as well as the 200 ml change in absolute volume for a significant bronchodilator response to be interpreted. This definition of a significant bronchodilator response has been recommended by ATS/ERS in their 2005 statement of the interpretation of lung function testing (Pelligrino, 2005). As is also stated in this report, there may be other definitions of a significant bronchodila-
tor response. As an example, the topic of bronchodilator response was discussed in a recent point and counterpoint series of articles (Pelligrino, 2014; Hansen, 2014). The counterpoint argument to using a 12% and 200 ml increase in FEV1, and FVC is that depending on the quality and precision of the spirometry data, much lower values of an increase may be statistically significant.

Both the ATS/ERS and GOLD spirometry guidelines recommend the use of post-bronchodilator FEV1, FVC, and FEV1/FVC to determine the presence of airflow obstruction. Spirometry after bronchodilators is believed to reduce variability in the measurement of FEV1 and FVC and improve testing repeatability (GOLD, 2014). In addition, post-bronchodilator measurements should provide maximal flow rates and, therefore, represent an individual’s “best” or greatest lung function. Even among individuals with normal lung function, the FEV1, FVC, and FEV1/FVC generally increase slightly after administration of a short acting beta-agonist and this effect diminishes with increasing age (Johannessen, 2006).

4.11 Summary Points

1. The identification of a patient with COPD has required the demonstration of airflow obstruction or airflow limitation as determined by spirometry testing.
2. If spirometry is performed, the testing must be done according to criteria of acceptability and repeatability as recommended by the American Thoracic Society and the European Respiratory Society.
3. The interpretation of spirometry test results involves the comparison of the actual measured values with predicted or reference values with normal vs abnormal results determined by the use of lower limits of normal (LLN) for the measured parameter.
4. Spirometry test results can be interpreted as different patterns: normal, airflow obstruction, possible restrictive lung defect or a mixed impairment pattern.
5. Airflow obstruction is present when the FEV1/FVC ratio is below the LLN or a value of 0.70 for that parameter. Borderline airflow obstruction may be present when there is a reduction in the mid-expiratory flow ratio.

References


Pelligrino R., Brusasco V. (2014) Point: Is an Increase in FEV$_1$ and/or FVC > 12% and > 200 mL the Best Way to Assess Positive Bronchodilator Response? Yes. Chest, 146(3), 536–537.


Key Points

1. Radiographic imaging can be complementary to lung function testing in the identification of patients with COPD.

2. Chest radiographs are useful as part of the initial evaluation of patients with respiratory symptoms but CT scans especially high-resolution CT scans (HRCT) can provide more information for the evaluation of the presence of emphysema, air-trapping, or smoking-related interstitial lung diseases.

3. PET Scans can discriminate malignant vs. benign lesions in patients with smoking histories who are found to have lung nodules by chest radiographs or CT scans.

4. Newer imaging techniques using MRI scans are being evaluated in research settings for functional analysis of smaller airways including airway wall size and distribution of air flow in patients with COPD.

5.1 Introduction

The use of radiographic imaging of the lungs is complementary to the use of lung function testing in the identification of patients with COPD. As part of the initial evaluation of patients who present with respiratory symptoms (dyspnea, cough, sputum production, chest tightness, wheezing, etc.), a routine chest radiograph is usually obtained. For most patients with COPD, this may be the only imaging study that is needed. For further evaluation of the presence and severity of the changes seen in patients with COPD, CT imaging can also be performed. This more advanced imaging is useful if abnormalities are identified by the chest radiograph or if other conditions related to smoking are being considered in the evaluation of the patient’s symptoms. Other advanced imaging techniques such as PET scanning or MRI scanning have some utility in COPD but are limited by cost and technical capabilities. However, ongoing research in these areas may ultimately provide a better understanding of relationships between distribution of ventilation and structure-function in patients with all severities of COPD including better estimation of disease progression and response to therapy (Coxson, 2014).

5.2 Chest Radiographs

Routine posterior-anterior (PA) and lateral views of the chest are standard images that can be ordered for patients who present with respiratory symptoms that may
besides identifying features of the lung that can be seen with COPD, the routine chest radiograph can be helpful to exclude other conditions such as lung cancer, heart failure and pneumonia.

Features of COPD that can be seen on routine posterior-anterior (PA) and lateral chest radiographs include 1) hyperinflation as noted by flattening of the diaphragms (especially noted on the lateral view) and increase in the retrosternal airspace (also seen on the lateral view) along with widening of the costophrenic angles (on the PA view), 2) presence of bullae that can be detected on standard images, and 3) tapering and reduction of the number of pulmonary vessels especially as they are seen in the lung periphery. An example of a standard chest radiograph for a patient with COPD is seen in Figure 5.1.

Other conditions that may be identified by chest radiographs in patients with COPD that present with acute symptoms include pleural effusions and pneumonia. Other smoking-related lung diseases (such as smoking-related interstitial lung diseases) may be suggested by chest radiographs but in most instances, further evaluation with more advanced imaging including CT scans is indicated.

5.3 Computed Tomography (CT) Scans

5.3.1 CT Scans and Emphysema

The value of CT scans in the further evaluation of patients with COPD has been well documented (Webb, 2009). This is especially true for the identification of the presence of emphysema (one of the two elements of COPD along with the clinical definition of
chronic bronchitis) (Friedman, 2008; Takahashi, 2008). Emphysematous regions of
the lung are defined as those areas that are 2 standard deviations below normal lung
parenchymal density (-750 to -850 Hounsfield Units (HU) with a threshold value of
-900 to -910 HU. In some studies, a threshold value of -950 HU is used. The presence
and extent of emphysema can then be categorized as: 1) less than 25% of the area, 2)
26 to 50% of the area, 3) 51 to 75% of the area or 4) 76 to 100% of the area examined.

Of the different forms of CT imaging, HRCT is the most sensitive method for iden-
tifying emphysematous changes. An example of emphysematous changes on a HRCT
is shown in Figure 5.2.

5.3.2 CT Scans and Air-trapping

Air-trapping is a pathophysiological term indicating the retention of excess gas in all
or part of the lungs at any stage of expiration. Air-trapping is a finding characteristic
of obstruction of the airways and is found in all forms of obstructive lung diseases
including asthma and COPD. There may be other associated pathological conditions
associated with air-trapping including bronchiectasis (which also may be seen in a
phenotype of COPD: see below) and interstitial lung disease (Miller, 2014).
In pulmonary function testing, air-trapping is the increase in residual volume (RV) or RV/TLC measurement compared to the predicted value. Radiographically, air-trapping is noted with CT scans with inspiratory and expiratory phases of imaging with the expiratory phase compared to the inspiratory images showing patchy areas of decreased lung attenuation consistent with air that has not been exhaled (Stern, 1994; Matsuoka, 2008). The Fleischner Society defines air-trapping as “parenchymal areas with less than normal increase in attenuation and lack of volume reduction” as seen on end-expiration CT scans” (Hansell, 2008). An example of the presence of air-trapping seen with an expiratory phase of a CT scan is shown in Figure 5.3.

5.3.3 CT Evaluation of Airway Changes in COPD

In addition to identifying the presence of emphysema, CT scans can identify other characteristics of COPD including airway luminal and airway wall changes that are characteristic of chronic bronchitis and bronchiectasis.
More recent techniques using CT scans have been able to measure airway luminal internal diameter and airway wall thickness in patients with COPD (Nakano, 2005; Patel, 2008). These methods require quantitative measurements of cross-sectional airway dimensions using transverse CT images (Lutey, 2013). Airways less than 2–3 mm in diameter are thought to be the location where the greatest changes occur for patients with COPD and the major site of airflow obstruction. Algorithms have been developed to take into consideration the oblique sectioning of airways on transverse images to arrive at better estimates of luminal diameter and airway wall thickness for these smaller airways. Further studies have shown good correlations between the airway changes and respiratory symptoms (Grydeland, 2010). In addition newer studies using MRI imaging with hyperpolarized helium-3 (He³) demonstrate regional gas distribution changes that correlate with the CT findings of the changes in these smaller airways (see later discussion regarding MRI imaging).

### 5.3.4 CT Scans for COPD Phenotypes

COPD might be best described by different phenotypes of presentation and illness (Vestbo, 2014). For example, there are the phenotypes of the frequent exacerbator (two or more exacerbations in the previous year), the overlap COPD-asthma phenotype, the emphysema-hyperinflation phenotype, and the bronchiectasis phenotype (Miravitlles, 2012; Martinez-Garcia, 2011). Several of these phenotypes are best described using CT scan results such as the emphysema and bronchiectasis phenotype presentations (Shah, 2014). The identification of bronchiectasis by CT scan has been defined previously by Naidich et al: air-fluid levels in distended bronchi, a linear array or cluster of cysts, dilated bronchi in the periphery of the lung and bronchial wall thickening due to peribronchial fibrosis (Naidich, 1982). An example of bronchiectasis as noted by CT scan is shown in Figure 5.4.

### 5.3.5 Lack of Correlation Between CT Findings and Spirometric Results for COPD

COPD is composed of two separate conditions: emphysema and airways disease represented by chronic bronchitis. Most patients with COPD will have some combination of these two pathological processes. The hallmark of airflow limitation in COPD is reduced maximal expiratory flow rates measured by spirometry. The pathological changes in the lungs that result in the reduced expiratory flow rates are 1) increased flow resistive properties of the airways (as in chronic bronchitis) and 2) reduced elastic recoil of the lung (as in emphysema). In COPD, the airways can be narrowed as a result of inflammatory changes and smooth muscle hypertrophy in the airway wall and increased amount of mucous and inflammatory material within the airway lumen. There is increased resistance to airflow as a result of the narrowed airway leading to
reduced flow rates for the same driving pressure that is generated to cause expiratory flow. In addition, loss of parenchymal tissue with emphysematous changes can reduce the support of airway walls contributing to airway narrowing and increased airway resistance. Also, the emphysematous changes reduce the elastic recoil and in turn the pressure gradient that is in part responsible for the generation of the expiratory flow rates.

However, recent studies suggest that the presence of airflow limitation noted by spirometry may not correlate well with the anatomic presence of emphysematous changes as noted on CT scans. In an editorial referring to this disconnect, Dr. James Hogg (Hogg, 2012) noted that the pathological process that leads to emphysema “in which the destructive process rapidly extends along surviving distal conducting airways to initiate emphysematous destruction of the alveolar surface...can account for the appearance of emphysema before a sufficient number of small airways have been destroyed to cause a reduction in FEV₁.”

5.3.6 CT Scans for Smoking-related Interstitial Lung Diseases

As mentioned above, CT scans are also useful when there may be other smoking-related changes in the lungs. These other abnormalities can include smoking-related interstitial lung disease (ILD) and lung cancer.
An example of the usefulness of CT scans in identifying the presence of smoking-related ILD is the finding of Smoking-related Respiratory Bronchiolitis with Fibrosis as described by Reddy and Churg (Reddy, 2013). They described a CT pattern of patchy areas of reticular changes about upper zone emphysematous spaces in individuals who do not have evidence of a diffuse ILD.

Other smoking related ILDs that have been defined using CT scan findings include Desquamative Interstitial Pneumonia (DIP), Respiratory Bronchiolitis-Interstitial Lung Disease (RB-ILD), Pulmonary Langerhans Cell Histiocytosis (PLCH) and even Idiopathic Pulmonary Fibrosis (IPF) which may occur more frequently in current and former smokers (Webb, 2009).

5.3.7 Use of Low Dose CT Scans for Surveillance for Lung Cancer

As also mentioned, CT scans can be used for the identification of other lung abnormalities in smokers especially the finding of bronchogenic carcinoma. The U.S. Preventive Services Task Force (among other professional societies) has recommended annual screening for lung cancer with low-dose CT scans in adults ages 55 to 80 years who have a 30 pack-year smoking history and who currently smoke or have quit within the past 15 years (Moyer, 2014).

5.4 Other Advanced Imaging Techniques in COPD

5.4.1 PET Scans

Positive emission tomography or PET scan is an imaging technique that examines the metabolic activity of lesions throughout the body that have been identified by other imaging techniques. A radiotracer such as fluorodeoxyglucose (FDG) that contains both sugar and radioactive elements is injected into the individual who is then scanned to detect those areas that have taken up and metabolized the sugar moiety and are radioactive. PET scans can differentiate malignant lesions (which are highly metabolically active) and benign lesions such as scars or fibrotic areas that are not active. If the lesion is an inflammatory process such as an active infection, it may also take up the radiotracer and be PET scan positive. The role of PET scanning in COPD is mostly for those patients who have a smoking history and have had nodules or other abnormalities identified by routine chest radiographs or CT scans. The PET scan can then be helpful in discriminating a malignant lesion from a benign lesion in these patients.
5.4.2 MRI Scans

1. As mentioned above in the section on CT Evaluation of Airway Changes in COPD, there are newer imaging techniques being evaluated in research settings using magnetic resonance imaging (MRI) scanning. Helium-3 (He3) and xenon-129 (Xe129) are gaseous magnetic resonance (MR) contrast agents that can be inhaled, permitting visualization of lung airspaces in an MR image (Salerno, 2001; Moller, 2002; van Beek, 2004). The MR signal from these hyperpolarized gases is easily detected using an MR scanner tuned to the appropriate resonance frequency.

2. MRI of hyperpolarized gases has led to the development of unique strategies for evaluating the structure and function of the lung (Salerno, 2001; Moller, 2002; van Beek, 2004). In particular, the relatively high solubility of xenon in biological tissues (Abraham, 1985), and an exquisite sensitivity to its environment that results in an enormous range (~200 ppm) of chemical shifts upon solution (Miller, 1981), make hypXe129 particularly attractive for exploring certain characteristics of lung function, such as gas exchange and uptake (Sakai, 1996). The quantitative characteristics of exchange and uptake are determined by physiologic parameters, including the surface-to-volume ratio and the thickness of the blood-gas barrier (Driehuys, 2006).

3. Since the primary function of the lung is gas exchange, impaired gas transport or exchange in subjects with pulmonary disease such as COPD can cause symptomatic shortness of breath. Non-equilibrium xenon uptake spectroscopy (NEXUS) can quantify the gas transport from the major airways all the way down to the alveolar gas exchange sites with high temporal resolution. In addition, chemical shift saturation recovery (CSSR) MR spectroscopy can be employed to measure the alveolar septal wall thickness and surface-to-volume ratio, both potentially highly relevant physiological parameters for the characterization of lung function in these patients with obstructive airways disease.

5.5 Summary Points

1. To better understand the pathophysiology of COPD including the impact of the disease for the patient and response to therapy requires more information than lung function test results. This additional information can be obtained with currently available imaging technology and other techniques now being developed.

2. Screening chest radiographs have limited usefulness but more advanced techniques such as CT scans (and in the future MRI scanning using polarized gases) can provide more helpful information including insight into the development and progression of COPD. Also, newer imaging techniques may inform us about the patient’s response to therapy that cannot be measured by standard pulmonary function testing.
References


6 Pathogenesis of COPD

Key Points
1. The pathogenesis of COPD is a complex, multifactorial process that includes genetics, proteolytic imbalance, oxidative stress, inflammation, occupational and environmental exposures, and innate and adaptive immune function.
2. Excessive secretion of proteases and inhibition of antiproteases contribute to the degradation of lung extracellular matrix.
3. Oxidative stress can directly injure alveolar epithelial cells and induce mucus secretion of airway epithelial cells.
4. The chronic inflammation that defines COPD is a strong correlate of disease severity in patients and is critically involved in disease development experimentally.
5. The pathogenesis of COPD includes extrapulmonary manifestations including systemic inflammation, cardiovascular disease, nutritional abnormalities and skeletal muscle dysfunction.

6.1 Introduction

Pathologically, COPD is defined as a combination of emphysema, small airway disease (fibrosis, scarring, increases in smooth muscle surrounding the airways), and chronic bronchitis (inflammation and mucus hypersecretion). The extent of each condition varies within individual patients (Barnes, 2003; Chung, 2008; Cosio, 2009). These pathological conditions affect both the large and small airways, as well as the lung parenchyma. The reduction in lung elasticity caused by the destruction of alveoli (emphysema) produces a loss of support and closure of the small airways during expiration (Barnes, 2004). Additionally, the small airways are physically narrowed by fibrotic scarring and an increase in the surrounding smooth muscle mass. This obstruction to airflow diminishes expiratory alveolar emptying and produces air trapping and hyperinflation (Barnes, 2004). Finally, a mucus-rich inflammatory exudate clogs the airways augmenting airflow resistance (Barnes, 2004). Together, these changes contribute to airflow obstruction that causes a reduction in normal lung function, measured as FEV₁ (forced expiratory volume in 1 second). In addition, COPD is associated with multiple other pulmonary diseases such as fibrosis, asthma, and lung cancer.
6.2 Chronic Bronchitis

Chronic bronchitis is defined clinically as a productive cough of greater than 3 months duration for more than two successive years, and is characterized by inflammation and excessive mucus production. The role of airway inflammation in COPD forms the basis of our current understanding of the pathogenesis of COPD and is elaborated upon in detail below. In COPD, mucus overproduction can physically plug the airways, and mucus hypersecretion is associated with a decline in FEV₁ (Prescott, 1995; Vestbo, 1996). Further, a role for mucus production in COPD is supported by the specific observation that accumulation of inflammatory exudates and mucus in the small airways increases with disease severity (Hogg, 2004). Mechanistically, it is believed that mucus/goblet cell hyperplasia and cellular phenotype alterations caused by cigarette smoking are the major causes of mucus hypersecretion in COPD (Innes, 2006).

6.3 Emphysema

Emphysema is characterized by a loss of lung elasticity (increased pulmonary compliance) caused by parenchymal lung destruction. Smoking causes both panacinar (destruction of parenchymal alveoli) and centriacinar (destruction around respiratory bronchioles) emphysema (Kim, 1991). Emphysema is a significant contributor to airflow obstruction in COPD and several studies have demonstrated correlations between the severity of macroscopic emphysema and measurable lung function decline (Hogg, 1994; Nakano, 2000). The causes of emphysema are multifactorial, but the best studied hypothesis for the development of emphysema is a protease:antiprotease imbalance leading to the destruction of lung tissue (Chung, 2008). Another major mechanism causing emphysema is lung epithelial and endothelial cell apoptosis. Apoptosis may be caused by oxidative stress or the cytotoxic functions of activated lymphocytes (e.g. CD8+ T cells, NK cells) that release perforin and granzymes directly killing lung epithelial cells. Finally, increased cellular senescence and a failure of lung maintenance and repair after chronic cigarette smoke exposure may also contribute to the development of emphysema (Chung, 2008).

6.4 Smooth Muscle

The amount of smooth muscle surrounding the airways, defined by total area, is increased in COPD patients and the amount of smooth muscle inversely correlates with lung function (FEV₁) (Bosken, 1990; Cosio, 1980; Saetta, 1998). In patients with severe COPD (GOLD stages 3 and 4), the amount of smooth muscle may be increased as much as 50% (Hogg, 2004). It is not entirely known how, or whether, increases in
smooth muscle contribute to the development of COPD. However, it has been speculated that the release of smooth muscle-derived inflammatory mediators in response to cigarette smoke or increased contractility may be involved (Chung, 2008).

### 6.5 Fibrosis

In addition to increases in peri-airway smooth muscle mass in COPD patients, there is also a significant increase in collagen deposition and fibrotic scarring around the small airways (Chung, 2008; Hogg, 2004). The fibrotic process is believed to further restrict proper contractility of the airways during breathing, thus contributing to airflow obstruction (Hogg, 2004). It is not entirely known how the development of fibrosis proceeds, both transforming growth factor β (TGFβ) and connective tissue growth factor (CTGF) levels are elevated in the airways of COPD patients (de Boer, 1998; Takizawa, 2001). TGFβ may cause fibrosis by inducing the expression of CTGF, which in turn drives the production and deposition of collagen (Ihn, 2002).

### 6.6 Pathogenesis of COPD

#### 6.6.1 Genetics: Gene-association Studies

Early studies estimated that only 10 to 15% of smokers develop COPD (Rennard, 2006). However, as early COPD is often asymptomatic, it is believed that COPD is significantly underdiagnosed (Coultas, 2001). More recent studies estimate the prevalence of COPD is as high as 20% and that up to 50% of smokers may have spirometric evidence of airflow obstruction (Buist, 2008; Halbert, 2006; Stang, 2000). Most lifelong smokers will develop COPD eventually, provided they do not die from nonpulmonary smoking-related diseases first (e.g. cardiovascular disease, metabolic disease, cancer) (Rennard, 2006). However, a small proportion of individuals will develop very severe COPD even after only smoking for a relatively short period of time (or as lifelong never smokers). The appreciation that the development of COPD in individuals with similar smoking histories is heterogeneous has led to fervent investigation into genetic risk factors that contribute to disease development. The first gene associated with the development of COPD was the α1-antitrypsin gene. Individuals who smoke and are homozygous for mutations of this gene develop severe COPD at a very early age. However, only about 1–2% of all COPD patients have this particular deficiency (Wan & Silverman, 2009). Studies involved in the identification of additional genes that confer susceptibility to COPD have been difficult due to the extreme phenotypic heterogeneity among COPD patients (Wan, 2009). Therefore, nonreplication of genetic association studies is extremely commonplace in COPD studies (Wan, 2009). However, there are a number of genetic associations that have been sufficiently rep-
licated across several labs. Replicated gene-association studies have identified proteases (MMP9, MMP12), detoxification/oxidative stress genes (EPHX1, HMOX1, GSTP1), genes involved in the immune response (TNFα, GC), and genes regulating apoptosis (TGFβ) as genes associated with development of COPD (Wan, 2009).

### 6.6.2 Epigenetics

In addition to classical gene-association studies, epigenetic control of gene expression is thought to be involved in COPD. However, as the field itself is relatively new, there are few studies that address this issue in COPD. Histone acetylation typically enhances gene transcriptional activity, and acetylation status is controlled by an enzyme that removes acetyl groups called histone deacetylase. With increasing disease severity, there is a corresponding decrease in overall histone deacetylase activity (increased histone acetylation) in the lungs of COPD patients (Ito, 2005). Therefore, this increased acetylation is believed to increase the transcriptional activity of proinflammatory genes in COPD patients. Supporting this hypothesis, COPD patients exhibit increased levels of histone acetylation and IL-8 expression (Ito, 2005). These observations are supported by animal studies in smoke exposed rats that demonstrate decreased histone deacetylase activity, increased histone acetylation, and enhanced NF-κB binding (Marwick, 2004). It is believed that histone deacetylase activity is reduced due to ubiquitination and subsequent degradation after cigarette smoke exposure (Adenuga, 2009).

### 6.6.3 Protease: Antiprotease Imbalance

The most well-studied mechanism of COPD pathogenesis is an imbalance in pulmonary protease and antiprotease levels. This hypothesis developed from the observation that some smokers with reduced levels of α1-antitrypsin develop emphysema at a very early age. However, these individuals only represent a very small minority of COPD patients (1–2%). Many COPD patients develop a protease:antiprotease imbalance through the overproduction of proteases by activated neutrophils and macrophages (Barnes, 2003). Proteases are important for the development of emphysema because these enzymes, particularly elastin, physically digest the extracellular matrix. A role for proteases in COPD development is supported by the demonstration that the instillation of a number of different proteases into the lungs of animals produces significant emphysema (Barnes, 2003). Elastase derived from neutrophils has received significant attention because it is the molecular target of α1-antitrypsin. Levels of neutrophil elastase are increased in COPD patients and instillation of neutrophil elastase into rodent lungs induces emphysema (Barnes, 2003). In addition to physical destruction of the airways, neutrophil elastase is also believed to be involved in inflammatory
cell recruitment and mucus production (Barnes, 2003). Further, chemical inhibition of neutrophil elastase prevents inflammation and emphysema in guinea pigs exposed to cigarette smoke (Table 6.1) (Wright, 2002). Although neutrophil elastase has received a significant amount of attention, a broad range of proteases are activated in COPD. Increased concentrations of cysteine proteases (cathepsins) have been observed in COPD patients, and chemical inhibition in rodent models prevents the development of a number of COPD phenotypes (Table 6.1) (Barnes, 2003). Further, matrix metalloproteinases (MMPs) may also be involved in disease development as a number of MMPs are upregulated in COPD patients and MMP knockout mice exposed to cigarette smoke are protected from the development of COPD phenotypes (Table 6.1) (Barnes, 2003).

6.6.4 Oxidative Stress

Cigarette smoke contains $10^{17}$ oxidant molecules per puff and is a significant source of reactive oxygen and reactive nitrogen species (ROS and RNS) (MacNee, 2000). There is considerable evidence of elevated oxidative stress in the lungs of cigarette smokers and there is an even greater increase in individuals with COPD (MacNee, 2005). The evidence in COPD patients includes increased levels of exhaled $\text{H}_2\text{O}_2$, 8-isopostane, and NO, all indirect measures of oxidative stress (MacNee, 2005). Additionally, COPD patients exhibit a decrease in plasma antioxidants, and an increase of oxidized lipids and proteins in plasma and tissues (MacNee, 2005). Based upon this evidence, it has been proposed that oxidative stress may be critical to the development and progression of COPD. Mechanistically, oxidative stress is believed to contribute to a number of important COPD phenotypes. Inactivation of α1-antitrypsin occurs by oxidation and a decrease in antiprotease activity is observed in bronchoalveolar lavage (BAL) fluid obtained after smoke exposure. Therefore, it is believed that physical inactivation of antiproteases by oxidative stress may significantly contribute to the protease:antiprotease imbalance in COPD patients (MacNee, 2005). Oxidative metabolites can induce the secretion of mucus from airway epithelial cells, and therefore, may be involved in mucus hypersecretion in COPD (Adler, 1990). Also, direct cell death of alveolar epithelial cells induced by oxidative stress has been proposed as a significant mechanism in the development of emphysema (MacNee, 2005; Petrache, 2005). Because oxidative stress can induce the expression of pro-inflammatory cytokines as well as chemotactic proteins, oxidative stress caused by cigarette smoke exposure may also be involved in the inflammatory response in COPD patients (MacNee, 2005).

A role for oxidative stress in COPD is strongly supported by animal models of COPD (Table 6.2). Therapeutic administration of antioxidants or transgenic overexpression of antioxidant genes decreases both the inflammatory response as well as the development of emphysema following cigarette smoke exposure (Foronjy, 2006;
### Table 6.1: Role of protease:antiprotease imbalance in mouse models of COPD.

<table>
<thead>
<tr>
<th>Species</th>
<th>Manipulation</th>
<th>Cigarette Smoke Exposure</th>
<th>Inflammatory Response</th>
<th>Development of Emphysema</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guinea Pig</td>
<td>serine protease inhibitor</td>
<td>6 months</td>
<td>decreased vs. untreated</td>
<td>Partial Protection~50% vs. untreated</td>
<td>decreased matrix breakdown products in BAL</td>
<td>(Wright et al., 2002)</td>
</tr>
<tr>
<td>mouse (C57BL/6)</td>
<td>α1-antitrypsin injection</td>
<td>6 months</td>
<td>decreased vs. untreated</td>
<td>Partial Protection~70% vs. untreated</td>
<td>decreased matrix breakdown products in BAL</td>
<td>(Churg, Wang, Xie, &amp; Wright, 2003)</td>
</tr>
<tr>
<td>mouse (C57BL/6)</td>
<td>NE-/−</td>
<td>6 months</td>
<td>decreased vs. WT</td>
<td>Partial Protection~60% vs. WT</td>
<td></td>
<td>(Shapiro et al., 2003)</td>
</tr>
<tr>
<td>mouse (C57BL/6)</td>
<td>MMP-12-/-</td>
<td>6 months</td>
<td>decreased macrophages, but not neutrophils vs. WT</td>
<td>complete protection vs. WT</td>
<td></td>
<td>(Hautamaki, Kobayashi, Senior, &amp; Shapiro, 1997)</td>
</tr>
<tr>
<td>Pallid Mouse</td>
<td>α1-antitrypsin deficient</td>
<td>6 months</td>
<td>CD4+ increased</td>
<td>Significant Increase vs. WT at 4 months</td>
<td></td>
<td>(Takubo et al., 2002)</td>
</tr>
<tr>
<td>Pallid Mouse</td>
<td>α1-antitrypsin deficient</td>
<td>6 months</td>
<td>not reported</td>
<td>Significant Increase vs. WT at 4 months</td>
<td></td>
<td>(Cavarra et al., 2001)</td>
</tr>
<tr>
<td>Guinea Pig</td>
<td>broad spectrum MMP inhibitor</td>
<td>6 months</td>
<td>decreased vs. untreated</td>
<td>Partial Protection~30% vs. untreated</td>
<td></td>
<td>(Selman et al., 2003)</td>
</tr>
<tr>
<td>Guinea Pig</td>
<td>MMP-9 and -12 inhibitor</td>
<td>6 months</td>
<td>decreased vs. untreated</td>
<td>Partial Protection~70% vs. untreated</td>
<td>decreased matrix breakdown products in BAL and airway remodeling</td>
<td>(Churg et al., 2007)</td>
</tr>
<tr>
<td>mouse (C57BL/6)</td>
<td>MMP-9 overexpression</td>
<td>n/a</td>
<td>not reported</td>
<td>Significant Increase vs. WT at 1 year</td>
<td>loss of elastin associated with emphysema</td>
<td>(R. Foronjy et al., 2008)</td>
</tr>
<tr>
<td>mouse (C57BL/6)</td>
<td>Lung MMP-12 overexpression</td>
<td>n/a</td>
<td>Increased</td>
<td>Significant Increase vs. WT tumors developed over time</td>
<td></td>
<td>(Qu, Du, Wang, &amp; Yan, 2009)</td>
</tr>
</tbody>
</table>
Nishikawa, 1999; Smith, 2002). In mice, cigarette smoke exposure activates the NRF2 protein, a redox sensitive protein critical to the expression of detoxification and antioxidant genes (Rangasamy, 2004). In addition, a broad panoply of antioxidant genes is activated in a NRF2 dependent manner after cigarette smoke exposure (Rangasamy, 2004). Important to the pathogenesis of COPD, NRF2 deficient mice exposed to cigarette smoke have a significantly enhanced inflammatory response, develop more severe emphysema and increased lung apoptosis, and have significantly enhanced levels of oxidative stress relative to wild-type mice (Iizuka, 2005; Rangasamy, 2004). In agreement with this observation, lung specific deletion of KEAP1, an inhibitor of NRF2 activation, leads to an increased basal antioxidant status and decreased pulmonary inflammation after cigarette smoke exposure (Blake, 2009). In conclusion, oxidative stress likely contributes to the development of COPD through multiple mechanisms.

### 6.7 Airway Inflammation in COPD

The significance of chronic inflammation observed in COPD has been demonstrated experimentally (Table 6.3) (Cosio, 2009; Hogg, 2004; Rennard, 2006). Increased inflammation occurs throughout the lungs in the large and small airways, as well as in the parenchyma (Hogg, 2004). It is believed that the inflammation surrounding the small airways is the most significant contributor to airflow limitation (Hogg, 2004). Additionally, patients with severe disease who quit smoking exhibit sustained inflammation and lung function decline, further implicating inflammation as a critical process in COPD development and progression (Gamble, 2007; Turato, 1995). Detailed below are the known functions of specific inflammatory cells in the development of COPD. Although individual cell types contribute to disease development in a number of ways, numerous types of immune cells likely act in a collective, reciprocal manner to cause disease. In addition, identification of the specific functions and roles of each cell type in the pathogenesis of COPD will provide new therapeutic targets.
### Table 6.2: Role of oxidative stress in mouse models of COPD.

<table>
<thead>
<tr>
<th>Species</th>
<th>Manipulation</th>
<th>Cigarette Smoke Exposure</th>
<th>Inflammatory Response</th>
<th>Development of Emphysema</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guinea Pig</td>
<td>recombinant superoxide dismutase (SOD)</td>
<td>acute</td>
<td>significantly decreased vs. untreated</td>
<td>not measured</td>
<td>decreased IL-8 and NK-κB activation</td>
<td>(Nishikawa et al., 1999)</td>
</tr>
<tr>
<td>Rat</td>
<td>catalytic antioxidant</td>
<td>acute</td>
<td>significantly decreased vs. untreated</td>
<td>not measured</td>
<td>decreased MIP-2, airway metaplasia</td>
<td>(Smith et al., 2002)</td>
</tr>
<tr>
<td>Mouse (C57BL/6xCBA/J)</td>
<td>Transgenic overexpression of CuZnSOD (antioxidant)</td>
<td>12 months</td>
<td>decreased vs. WT</td>
<td>complete protection vs. WT</td>
<td>protects against lipid peroxidation</td>
<td>(R. F. Foronjy et al., 2006)</td>
</tr>
<tr>
<td>Mouse (ICR)</td>
<td>NRF2/-</td>
<td>6 months</td>
<td>significantly increased vs. WT</td>
<td>earlier and more severe</td>
<td>decreased apoptosis</td>
<td>(Rangasamy et al., 2004)</td>
</tr>
<tr>
<td>Mouse (BALB/c)</td>
<td>NRF2/-</td>
<td>4 months</td>
<td>significantly increased vs. WT</td>
<td>earlier and more severe</td>
<td>decreased TNFα</td>
<td>(Iizuka et al., 2005)</td>
</tr>
<tr>
<td>Mouse (C57BL/6)</td>
<td>Lung specific KEAP1/-</td>
<td>acute</td>
<td>significantly decreased vs. WT</td>
<td>not measured</td>
<td>Increased basal antioxidant genes</td>
<td>(Blake et al., 2009)</td>
</tr>
</tbody>
</table>

### 6.7.1 Epithelium

Alveolar and airway epithelial cells are important in the pathogenesis of COPD. Epithelial cells exposed to cigarette smoke produce a diverse array of inflammatory mediators including TNFα, IL-1β, GM-CSF, IL-8, MCP-1, and LTB4 (Masubuchi, 1998; Mio, 1997). Emphysema develops partly due to apoptotic cell death of the lung epithelial cells, possibly through the actions of cytotoxic lymphocytes or oxidative stress (Chung, 2008; Majo, 2001).

### 6.7.2 Neutrophils

The numbers of activated neutrophils, characterized by increased respiratory burst and granule enzyme release, are greatly increased in the sputum and BAL of COPD patients and smaller increases are detectable in the airways and parenchyma (Finkelstein, 1995; Keatings, 1996; Lacoste, 1993; Pettersen, 2002). The number of circulat-
ing and lung neutrophils correlates with the decline in FEV\textsubscript{1} and neutrophil numbers in induced sputum correlate with COPD severity, thus implicating them in disease progression (Baraldo, 2004; Keatings, 1996; Sparrow, 1984). It is likely these changes are induced by IL-8. IL-8 is chemotactic for neutrophils, activates neutrophils, and expression is increased in COPD patients (Barnes, 2003; Pettersen, 2002). It is unknown how neutrophils specifically contribute to disease progression, but neutrophils secrete a number of proteases important in COPD pathogenesis such as neutrophil elastase, cathepsin G, proteinase-3, as well as matrix metalloproteinase MMP-8 and MMP-9 (Barnes, 2003). Thus, neutrophils are believed to be crucially involved in tipping the protease:antiprotease balance to a more proteolytic environment within the lungs of individuals with COPD. This hypothesis is further supported by the observation that neutrophil elastase knockout mice are partially protected from disease development after cigarette smoke exposure (Table 6.1) (Shapiro, 2003). Interestingly, although neutrophils can cause an increase in proteases that can cause experimental emphysema, similar emphysematous destruction is not observed in other chronic pulmonary diseases dominated by neutrophils like cystic fibrosis and bronchiectasis (Barnes, 2003).

### 6.7.3 Macrophages

Macrophages are significant contributors to the pathogenesis of COPD. There is an overwhelming increase in the number of macrophages in the BAL and sputum, airways, and parenchyma in COPD patients (Barnes, 2003). Further, macrophages are localized to sites of tissue destruction in COPD (Finkelstein, 1995; Meshi, 2002) and there is a correlation of macrophages with the severity of disease (Di Stefano, 1998). Macrophages secrete a number of inflammatory mediators after exposure to cigarette smoke that may activate and recruit additional cell types (Barnes, 2003). Additionally, alveolar macrophages taken from COPD patients are intrinsically altered, and secrete more inflammatory mediators and have more proteolytic activity at baseline (Barnes, 2003). Macrophages are also significant sources of destructive proteases MMP-2,-9, and -12, and cathepsin K, L, and S, that have key functions in the development of COPD in various mouse models (Table 6.1).

### 6.7.4 Eosinophils

In COPD patients, the number of eosinophils is increased in the sputum, BAL, and airway walls and there are elevated levels of eosinophil cationic protein in the BAL and sputum (Fujimoto, 1999; Lacoste, 1993; Lams, 1998; Linden, 1993; Panzner, 2003). Cytokines that are associated with eosinophilia in asthma, IL-4 and IL-5, are also upregulated in COPD (Zhu, 2007). During COPD exacerbations, the number of eosin-
Pathogenesis of COPD

Eosinophils is increased and IL-5 production is enhanced (Saetta, 1996; Zhu, 2001). It is unclear whether these increases in eosinophil numbers in COPD represent a distinct subgroup of patients with concomitant COPD and asthma, and it is equally unclear whether eosinophilia in COPD correlates to severity of disease. However, patients with enhanced numbers of eosinophils typically respond well to inhaled corticosteroids (Chanez, 1997; Pizzichini, 1998).

6.7.5 Mast Cells

Mast cells are present in the airways and alveoli of healthy individuals (Andersson, 2009b; Carroll, 2002) and have critical roles in innate immunity, T cell regulation, and antigen presentation. Despite the fact that these essential functions suggest that mast cells might have a pivotal role in COPD pathogenesis (Dawicki, 2007; Jawdat, 2006; Metz, 2008), very few studies have examined mast cell function in the context of COPD. Although increases in mast cells have been reported in the airways of COPD patients (Grashoff, 1997; Pesci, 1994), a more recent study demonstrated a reduction in mast cells in COPD patients, and that fewer numbers of mast cells correlated with worse lung function suggesting a protective, regulatory role for mast cells in COPD (Gosman, 2008). An additional study corroborates this finding and demonstrated that mast cell numbers decreased with increasing disease severity (Andersson, 2009a). In addition, these authors found that as COPD worsened, the mast cell populations in the lung underwent changes in density, distribution, and molecular phenotype implicating them in COPD pathogenesis (Andersson, 2009a).

6.7.6 γδ T Cells

Very little is known about the function of γδ T cells in COPD. γδ T cells are increased in the airways, bronchoalveolar lavage, and peripheral blood of smokers, regardless of whether they have emphysema (Ekberg-Jansson, 2000; Majo, 2001; Pons, 2005; Richmond, 1993). In some cases, the number of γδ T cells is reduced in patients with COPD compared with their levels in smokers (Pons, 2005). γδ T cells are important regulators of tissue repair and mucosal homeostasis (Jameson, 2003). Consistent with this role, the absence of γδ T cells caused enhanced caspase-dependent epithelial cell death in a mouse model of COPD, although inflammation was not affected (Borchers, 2008). Based upon these observations, not only are γδ T cell numbers reduced in COPD but their function may also be impaired.
6.7.7 Natural Killer (NK) Cells

There are few studies examining NK cells in COPD, and therefore the role of NK cells in COPD is relatively unknown. One study has shown no increases in NK cells in the lung parenchyma in COPD patients relative to controls, but this study was limited by small sample sizes (Majo, 2001). In contrast, two additional studies using a greater number of samples demonstrated an increase of NK cells in the lungs of COPD patients (Di Stefano, 1998; Elliott, 2009). Importantly, NK cell numbers correlated with disease severity (Di Stefano, 1998; Elliott, 2009). A major function of NK cells is their capacity for cell specific, directed cytotoxicity mediated through the release of perforin and granzymes that induce target apoptosis. Localized inflammatory sites in the lungs of COPD patients are rich with granzyme A+ and granzyme B+ NK cells (Vernooy, 2007). Additionally, the expression of NK cell perforin and granzyme B, as well as functional NK cell cytotoxic effector function, was shown to be increased in the sputum of COPD patients (Urbanowicz, 2009). In a corollary study, perforin and granzyme B expression was increased in peripheral blood NK cells of COPD patients and smokers (n=60) (Hodge, 2006), but this observation was not reproduced by two separate groups using a small number of patients (n=10) (Morissette, 2007). Therefore, it is likely that NK cells contribute to apoptotic cell death and the development of emphysema in COPD.

Recent data demonstrate an additional role for NK cells in COPD. In COPD patients, there is increased expression of MICA on the lung epithelium, a stress-inducible ligand for the NK cell activating receptor NKG2D (Borchers, 2009). Importantly, expression of MICA on the lung epithelium correlates with disease severity. Experimentally, chronic cigarette smoke exposure also induced expression of NKG2D ligands on the mouse airway and alveolar epithelium. These observations provide strong support for a role of NKG2D activation and NK cells, in particular, in the development of COPD. In contrast, there is some data suggesting that NK cells may be functionally suppressed in COPD.

6.7.8 Natural Killer T (NKT) Cells

A role for NKT cells in COPD is ill-defined and is limited by the overall paucity of studies. CD56+CD3+ NKT-like cell number and function is reduced in the peripheral blood of COPD patients (Urbanowicz, 2009). However, this report is severely limited by the use of very few patients (n=10), the majority of whom were using inhaled corticosteroids, a variable known to interfere with functional assays. In one study, no differences in the numbers of Type-1, invariant NKT (iNKT) cells were detected in the sputum of COPD patients with stable disease or during COPD exacerbations (Vijayanand, 2007). However, in a more recent study using immunohistochemistry, increased numbers of iNKT cells were found in the lungs of COPD patients. iNKT cells stimulate the production of IL-13 which drives alternative activation of macrophages.
and leads to macrophage generated IL-13 in a feed-forward loop. Persistent IL-13 production is believed to contribute to protease activation, mucus hypersecretion, and mucus cell hyperplasia, all important phenotypic changes in COPD.

6.7.9 T Cells

In COPD patients, there are increased numbers of T cells in the lung parenchyma and peripheral and central airways, and, in severe COPD, T cells are located within lymphoid follicles adjacent to airways (Cosio, 2002; Finkelstein, 1995; Hogg, 2004; Majo, 2001; O’Shaughnessy, 1997; Retamales, 2001; Saetta, 1999; Saetta, 1998). Similar to COPD patients, CD3+ T cells are organized in lymphoid follicles in mice chronically exposed to cigarette smoke, suggesting a common mechanism (Bracke, 2006). Although both CD4+ and CD8+ T cell numbers increase, the greatest elevation is in the CD8+ T cell population (Hogg, 2004; Majo, 2001; Saetta, 1999; Saetta, 1998). Significantly, the increase in CD8+ T cells directly correlates with lung function decline (Saetta, 1999; Saetta, 1998). There is also an increase in the number of CD8+ T cells in the peripheral blood of COPD patients who don’t smoke (de Jong, 1997; Kim, 2002). Further, peripheral T cells are more activated in COPD patients, and activation correlates with the loss of lung function (Zhu, 2009). Mouse models exhibit the hallmark features of COPD including mucus cell metaplasia, airspace enlargement and peribronchial/perivascular infiltration of neutrophils, macrophages, and T cells. In these models, CD8−deficient mice (but not CD4−deficient mice) fail to develop these key features of COPD, including macrophage accumulation and airspace enlargement (Borchers, 2007; Maeno, 2007). While evidence mounts supporting a causal role for T cells in COPD, the initial stimulus remains to be identified. The most likely mechanism driving T cell-mediated pathology is antigen-specific clonal expansion. In support of this theory, oligoclonal expansions of CD4+ and CD8+ T cells are detected in the lungs of COPD patients (Korn, 2005; Sullivan, 2005). Although the antigen specificity or function of T cells in COPD remains wholly uninvestigated, it is probable that oligoclonal expansions reflect recognition of self antigens. In support of this idea, T cells reactive with elastin have recently been demonstrated in COPD patients. It is unclear what role autoreactive T cells may play, but T cell recognition of antigens present on the lung epithelium may cause robust inflammation and the production of cytokines and chemokines in COPD (Enelow, 1998; Zhao, 2000). Presently, mechanistic data supporting a causal role for T cells in the development or progression of COPD are limited. Derangement of the alveolar architecture may be caused by multiple processes including matrix breakdown as well as epithelial and endothelial cell destruction. The prevailing theory is that T cells are aberrantly activated in COPD patients and contribute to tissue destruction through both direct and indirect effector mechanisms. The direct mechanisms likely involve CD8+ T cell-mediated apoptosis of alveolar cells via the elaboration of cytotoxic granules (perforin-
granzyme) or Fas molecules (Henkart, 1994). Along these lines, alveolar epithelial cell apoptosis correlates with CD8+ T cell numbers in emphysema (Majo, 2001) and this theory is supported by evidence that CD8+ T cells in patients with COPD express high levels of perforin with a concomitant enhanced lytic capacity (Chrysofakis, 2004). Indirect mechanisms whereby lymphocyte activation contributes to COPD are more complex and difficult to assess. However, a role for the broad inflammatory cell recruitment and activation in COPD patients and experimental models seems likely. For example, many studies indicate that the production of Th1 cytokines such as IFNγ (Di Stefano, 2004; Grumelli, 2004; Hodge, 2007) and TNFα (Aaron, 2001; Keatings, 1996) are increased in T cells of COPD patients. Di Stefano et al. reported that the number of STAT4-positive cells (a transcription factor critical for the development of Th1 lineage cytotoxic T cells) are increased compared to healthy smokers and non-smokers (Di Stefano, 2004). Furthermore, the number of STAT4+ lymphocytes correlated with increased airflow obstruction and IFNγ+ lymphocytes. In a more detailed study, Grumelli et al. demonstrated that lung function decline in patients with COPD correlated with Th1 cell markers on both CD4+ and CD8+ T cells, and these cells secreted increased amounts of IFNγ, but not IL-4, relative to control patients (Grumelli, 2004). IFNγ induction may amplify inflammation and increase macrophage metalloproteinase secretion which can lead to matrix degradation and alveolar destruction (Grumelli, 2004; Wang, 2000). Grumelli et al. (Grumelli, 2004) also provided a mechanistic link between increased T cell activation and emphysema by demonstrating enhanced production of CXCR3 ligands (i.e., IP-10) which leads to increased MMP-12 activation (elastin-degrading protease linked to emphysema) by alveolar macrophages. In addition to their pro-inflammatory effector function, sub-populations of CD4+ T cells (i.e., regulatory T cells) may also serve to limit the adaptive immune responses. In the context of COPD, a breakdown in the function of these cells may lead to increased expansion of pathogenic T cells.

6.7.10 B Cells

CD20+ B cells are increased in the lungs of COPD patients (Gosman, 2006; Hogg, 2004). Importantly, the number or presence of CD20+ B cells in airways and periphery correlates with disease severity (Gosman, 2006; Hogg, 2004). Most often, B cells are organized in lymphoid follicles in COPD patients that are interspersed with CD4+ and CD8+ T cells (Hogg, 2004; Kelsen, 2009; van der Strate, 2006). Interestingly, lymphoid follicles containing high numbers of B cells also develop in mice chronically exposed to cigarette smoke (Bracke, 2006; D’Hulst, 2005; van der Strate, 2006). Currently, it is unknown whether B cells are specifically required for the development of COPD. A primary function of B cells is the generation of antigen-specific antibodies. Differentiated antibody producing B cells, known as plasma B cells, also are increased in the lungs of COPD patients (J. Zhu, 2007), and B cells organized in lymphoid follicles were
identified as being oligoclonal, suggesting specific, antigen-directed antibody production (van der Strate, 2006). B cells are likely responding to self-antigens because, in addition to elastin-reactive T cells, elastin-reactive antibodies are present in COPD patients (Lee, 2007). Further evidence for a self-antigen comes from the observation that COPD patients have pulmonary epithelial cell-reactive antibodies (Feghali-Bostwick, 2008).

### 6.7.11 Dendritic Cells

Dendritic cells (DCs) are key cells in antigen presentation and bridge the gap between the innate and adaptive immune system. Increases in DCs occur in patients and mouse models of COPD (D’Hulst, 2005; Demedts, 2007; Freeman, 2009) and the DCs frequently have an activated phenotype (D’Hulst, 2005; Freeman, 2009). Maturation of DCs correlates with disease severity, strongly suggesting a mechanistic role for DCs in COPD (Freeman, 2009). Further, the expression of maturation markers correlates with the activation of CD4+ T cells in COPD patients (Freeman, 2009). However, evidence has accumulated for roles of DCs in COPD independent of their antigen presentation capabilities. Myeloid dendritic cells isolated from the lungs of COPD patients were able to induce Th1 and Th17 responses in the absence of antigen presentation (Shan, 2009). Additionally, in vitro exposure of dendritic cells to cigarette smoke extract induced the expression of inflammatory mediators leading to the activation and proliferation of co-cultured CD8+ T cells, providing a potential link between DCs and CD8+ T cell accumulation in COPD (Mortaz, 2009).

### 6.8 Cytokines and Chemokines in COPD

Cytokines and chemokines are involved in a diverse array of COPD phenotypes including the recruitment and activation of macrophages, neutrophils, T cells, B cells, and other immune cells. Cytokines and chemokines are also believed to be involved in the processes of airway remodeling, mucus cell hyperplasia, and emphysema. Therefore, the roles of cytokines and chemokines in COPD are multitudinous. CCL1/I-309, CCL2/MCP-1, CCL3/MIP-1α, CCL4/MIP-1β, CCL11/eotaxin, CXCL1/GROα, CXCL5/ENA-78, CXCL8/IL-8, IL-1β, IL-6, IL-18, IFNγ, IP-10, GM-CSF, and TNFα are among the many cytokines and chemokines that are increased in individuals with COPD (Chung, 2008). These increases are detected in the lung tissue, sputum, or the BAL fluid, and the levels of cytokines and chemokines frequently correlate with disease severity (Chung, 2008). These cytokines and chemokines are frequently derived from a number of resident inflammatory cells as well as the airway epithelium (Chung, 2008). In addition to the cytokines mentioned here, a number of additional cytokines and chemokines are undoubtedly increased in COPD but have yet to be studied. The study of cytokine and
chemokines in the development of COPD phenotypes has been aided using mouse models of COPD. Studies utilizing mice that have had either cytokines/chemokines or their receptors knocked out are almost always protected from the development of emphysema, and have reduced inflammation after smoke exposure. Conversely, a number of studies have utilized mice that overexpress proinflammatory cytokines/chemokines explicitly in the lung, and these mice develop COPD-like disease (emphysema and inflammation).

### 6.9 COPD as an Autoimmune Disease

Autoimmune diseases are chronic inflammatory conditions caused by failure of self-tolerance mechanisms. Although it is not completely understood how this breakdown occurs, it likely results from a complex interplay of genetics, failure of natural tolerance, and environmental triggers. The defining criteria for autoimmune diseases are classically defined by Witebsky’s postulates (Rose, 1993) a) circumstantial evidence consisting of lymphocytic infiltration of the target organ or association of the disease with a particular MHC haplotype, b) indirect evidence consisting of the isolation of autoantibodies or self-reactive T cells from the organ or identification of human antigen and using immunization processes to reproduce the disease in animals, and finally, c) direct proof consisting of reproducing the disease in a normal recipient by the direct transfer of autoantibodies or T cells. Based on the associations of T cell numbers with declining lung function in COPD patients and evidence that inflammation persists in COPD patients upon smoking cessation (Gamble, 2007; Turato, 1995), Cosio and colleagues proposed the existence of an autoimmune component in COPD (Cosio, 2002; Cosio, 2009). Since then, multiple lines of evidence have accumulated supporting this hypothesis. As mentioned above, oligoclinal T cells and B cells that can react with self-antigens have been identified. Recent evidence that maturation of dendritic cells correlates with T cell activation COPD further supports this hypothesis (Freeman, 2009). In addition, single nucleotide polymorphisms in multiple HLA loci associate with the severity of COPD (DeMeo, 2008). Therefore, since the early hypothesis, a significant body of evidence has accumulated suggesting that COPD has an autoimmune component. Moreover, the possibility exists that the cigarette smoke-induced autoreactivity may have broader implications for systemic manifestations of COPD as cigarette smoking has been identified as a risk factor for established autoimmune diseases such as rheumatoid arthritis (Papadopoulos, 2005), Graves disease (Prummel, 1993), and biliary cirrhosis (Gershwin, 2005).
6.10 Systemic Inflammation

The presence of low-grade systemic inflammation is a well-known characteristic of COPD (Agusti, 2003; Gan, 2004). Patients with stable COPD have an increased numbers of circulating leukocytes occasionally present with an activated phenotype (Noguera, 2001; Noguera, 1998). Further, activation of circulating lymphocytes correlates with lung function (Zhu, 2009). Further, COPD patients have increased circulating levels of inflammatory mediators such as C-reactive protein, fibrinogen, IL-6, and TNFa (Agusti, 2003). Additionally, the severity of this inflammation is increased during exacerbations of COPD (Hurst, 2006). Because COPD is overwhelmingly associated with an abnormal inflammatory response in the lungs, it has been proposed that the systemic inflammatory response is simply the result of a spilling over effect from the lungs (Agusti, 2007). However, several investigators were unable to find relationships between inflammation using specific measured variables in the lungs and blood of individual patients (Hurst, 2005; Vernooy, 2002). Therefore, it's really unknown whether a spillover is really a sufficient explanation. Interestingly, several extrapulmonary diseases frequently associated with COPD are also associated with a systemic inflammatory response (Agusti, 2007).

6.10.1 Cardiovascular Disease

COPD and cardiovascular disease (CVD) share the common risk factor of cigarette smoking. Additionally, COPD and CVD patients share commonalities such as advanced age and decrease in physical activity. However, several lines of evidence have established that, independent of known risk factors including smoking, COPD correlates as an independent risk factor for CVD (Rodriguez-Roisin, 2008; Sin, 2006). COPD is a significant risk factor for a broad spectrum of CVD manifestations such as atherosclerosis, ischemic heart disease, stroke and sudden cardiac death (Sin, 2006). In patients with mild COPD, complications from CVD are overwhelming the cause (42%) for first time hospitalization (Rodriguez-Roisin, 2008; Sin, 2006). In contrast, respiratory complications are the cause for only 14% of hospitalizations. Most important, CVD is extremely important in COPD as between 25–50% (depending on the study) of all COPD deaths are due to complications of cardiovascular disease (Rodriguez-Roisin, 2008; Sin, 2006). The exact mechanisms involved in cardiac disease in COPD patients are unknown. As described above, patients with COPD have significant levels of systemic inflammation. Systemic inflammation is a key risk factor for the development of CVD (Buffon, 2002). Because systemic inflammation is a common feature in patients with COPD, even in mild to moderate stages, it has been suggested by multiple investigators as a key component of CVD risk. Particularly, increased levels of C-reactive protein is significant risk factor for combined COPD and CVD (Sin, 2003). More work is needed in this area.
6.10.2 Nutritional Abnormalities

Divergent Weight Loss and Obesity in COPD. Numerous nutritional abnormalities have been detected in patients with COPD (Nici, 2006; Schols, 2000). Changes in the basal metabolic rate, caloric intake, and body composition are common in patients with COPD (Nici, 2006; Schols, 2000). Weight loss with no apparent explanation occurs in about half of patients with severe COPD, but is also detected in about 15% of COPD patients with mild to moderate disease (Creutzberg, 1998; Nici, 2006). It is believed that weight loss is not due to loss of fat, rather the majority of loss is in skeletal muscle mass (Schols, 2000). Further, recent weight loss is a significant predictor of future mortality and morbidity (Nici, 2006). Although these changes may be responsible for changes in caloric intake, increases in basal metabolic rate from medications, systemic inflammation, and/or tissue hypoxia have been proposed (Agusti, 2005).

Briefly, metabolic syndrome is characterized by a multitude of factors including abdominal obesity, atherogenic dyslipidemia, hypertension, and insulin resistance (Watz, 2009). In contrast to the description of weight loss above, a significant number of COPD patients have coexisting metabolic syndrome or obesity (Watz, 2009; Franssen, 2008). Further, obesity is more prevalent in patients with COPD than in the general population (Franssen, 2008). Interestingly, the metabolic syndrome and obesity in COPD patients was associated with increases in markers of systemic inflammation CRP and IL-6 (Watz, 2009). Further, in this study there was a correlation between an increase in severity of COPD and a lower BMI (Watz, 2009). Studies have demonstrated that patients with a predominance of chronic bronchitis are more likely to have a higher BMI, whereas patients with predominantly emphysema will have a lower BMI (Ogawa, 2009). Whatever the mechanism behind the obesity-COPD relationship, obesity nonetheless is a major problem for COPD patients as obese patients are frequently exercise intolerant, a major problem for exercise-based pulmonary rehabilitation therapies (Franssen, 2008).

6.10.3 Skeletal Muscle Dysfunction

Skeletal muscle dysfunction is extremely common in COPD patients (Nici, 2006). There are specific anatomic changes as well as functional changes (Nici, 2006). The precise mechanism underlying muscle wasting is unknown, but could be due to inactivity-induced deconditioning, systemic inflammation, use of medications, oxidative stress or reductions in muscle mass (Nici, 2006). Although little is known in on this topic, these changes significantly contribute to loss of exercise capacity critical for pulmonary rehabilitation and a reduction in the quality of life (Nici, 2006).
6.10.4 Osteoporosis

The incidence of osteoporosis is also increased in patients with COPD. The specific causes are unknown, but have been speculated to be caused by malnutrition, smoking, steroid use, lack of exercise, and systemic inflammation (Agusti, 2003). However, little is known about osteoporosis in COPD beyond that.

6.10.5 Neurological Disorders

There are significant alterations in the nervous system in patients with COPD. The actual bioenergetic metabolism of the brain is altered in patients with COPD (Mathur, 1999). Importantly, COPD patients frequently suffer depression (Light, 1985; Xu, 2008; Maurer, 2008). The depression and anxiety in COPD have been found to be important and serious risk factors for disease progression (Xu, 2008). It’s likely that depression develops in response to having a chronic disease. However, it’s been proposed that systemic inflammation may also be involved (Agusti, 2003).

6.11 COPD Exacerbations

The underlying COPD pathologies are punctuated by exacerbations of symptoms. Standard criteria for COPD exacerbations do not exist, but they are generally characterized by increased dyspnea, enhanced sputum, enhanced inflammation, and decline in lung function (Bhowmik, 2000; Sapey, 2006), (see Chapters 16, COPD Exacerbations Outpatient Management, and 17, COPD Exacerbations Inpatient Management). Consequently, exacerbations accelerate disease progression and are an integral part of disease pathogenesis. The toll of COPD exacerbations is also psychologically destructive; patients with frequent exacerbations have a lower quality of life and decreased mobility, leading to increased depression (Quint, 2008). Most importantly, exacerbations that require hospitalization result in death 8–11% of the time, and the remaining patients have a mortality rate of 23–43% one year following admission (Connors, 1996; Groenewegen, 2003). Between 40 and 60% of exacerbations are believed to be caused by viral infections (Celli, 2007; Sapey, 2006). The remaining exacerbations are likely the result of non-viral infections and pollution, although roughly 20% have an unknown etiology (Celli, 2007). Exacerbations associated with viral infections are severe; viral exacerbations lead to hospitalization more often than other causes, and have a longer recovery time (Wedzicha, 2004). The connection between viruses and COPD exacerbations remained mostly associative until, in a recent landmark study, Kang et al. experimentally demonstrated that exacerbations of symptoms following cigarette smoke (CS) exposure can be caused by viral infection (Kang, 2008). Key to the progression of COPD, viral infection following CS
exposure led to enhanced pulmonary inflammation, increased alveolar apoptosis, accelerated emphysema, and airway fibrosis (Kang, 2008). However, the underlying cellular mechanisms responsible for these effects remain undiscovered.

### 6.12 Summary Points

1. The pathophysiology of COPD is incompletely understood, but is thought to involve chronic inflammation, oxidative stress, and increased elastolytic potential in the lung.
2. Increased numbers of macrophages, neutrophils, lymphocytes and eosinophils in and around the airways, parenchyma, and vasculature characterize the inflammation. Pathogenesis of COPD is examined mechanistically. Current and future research into the pathways that lead to COPD will provide insight into much needed therapeutic targets.
3. COPD also manifests systemically including systemic inflammation, skeletal muscle dysfunction, metabolic syndrome, cardiovascular disease, osteoporosis, and neurological defects.
4. Enhanced understanding of the role of the immune system in acute exacerbations in COPD is critical in the future identification of susceptible patients and the development of new therapeutic strategies.

### References


Pathogenesis of COPD


References


7 Smoking Cessation

Key Points:
1. Smoking cessation is the single most important approach to preventing and treating COPD.
2. Abstinence from smoking tobacco is associated with a variety of health improvements, including decreased mortality and reduced risk of developing lung cancer, myocardial infarction, and stroke.
3. Patients should be screened for tobacco use at every visit; patients who do use tobacco products should be asked about any smoking-related concerns and desire to stop smoking.
4. It is important to investigate a patient’s stage-of-change when discussing smoking cessation and ask questions that are appropriate to the patient’s current stage.
5. Nicotine replacement therapies and other tobacco treatment medications, used either alone or in combination with counseling, lead to the highest cessation rates.

7.1 Introduction

Smoking-related deaths and diseases are preventable but continue to affect a considerable number of individuals. Tobacco use is thought to be responsible for more than 438,000 premature deaths each year in the United States and is considered to be one of the main risk factors responsible for the development of Chronic Obstructive Pulmonary Disease (COPD). Although there are other causes of COPD, 80–90% of those (in the United States and the developed world) who have been diagnosed with COPD are current or past smokers (Rabe, 2007). Parker and Eaton (2012) suggest that the most important approach to preventing and treating COPD in current smokers is smoking cessation. They also suggest that smoking cessation is the only evidenced-based treatment that makes impactful physical changes in multiple areas of functioning (i.e., reduces the accelerated rate of lung function decline, decreases symptoms of cough and sputum, and reduces COPD exacerbations). Their research also indicates that smoking cessation is associated with a short-term increase in lung function (up to 50 mL increase in the forced expiratory volume in one second, FEV1), which lasts approximately one year, followed by a continued decline in lung functioning at the rate of a nonsmoker.

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7.2 Smoking Risks

The risks of increased disability and premature death for smokers who have COPD is reflected in Figure 7.1 (Lung Age Graph; Panos, 2014). The graph also depicts improvements in longevity and health that might be gained when one stops smoking. Research indicates that complete abstinence from tobacco decreases mortality and reduces the risks of developing lung cancer, myocardial infarction, and stroke (Anthonisen, 2005). Non-smokers who have COPD can experience disease exacerbations, including increased cough and sputum production, if exposed to passive smoke (Leuenberger, 1994). Complete elimination of exposure to tobacco smoke, whether active or passive, is recommended.

7.3 Factors Associated with Cessation

COPD develops after years of tobacco use. Approximately 50% of current smokers over the age of 75 have COPD (Lundback, 2003). Older age, along with the duration and severity of nicotine dependence, add to the challenges of quitting (Tashkin, 2001).
A chronic illness model is often used to conceptualize tobacco use (Burke, 2008). Smoking cessation is a process that occurs across a series of attempts that finally culminate in permanent abstinence. Smokers often relapse after quitting; half of the patients who reach six months of abstinence will smoke again within eight years (Yudkin, 2003). Thus, ongoing assessment and relapse prevention are important even after a patient successfully quits. It is recommended that healthcare providers continue to engage with patients who have experienced a smoking relapse, similar to how patients who have poorly-controlled hypertension or diabetes are treated.

7.4 Screening Recommendations

The Clinical Practice Guideline for Treating Tobacco Use and Dependence (henceforth known as Clinical Practice Guideline; U.S. Department of Health and Human Services, 2008) recommends that all patients be screened for tobacco use at every visit. Screening is especially critical for patients who are at risk for or have been diagnosed with COPD. This recommendation applies to all healthcare professionals (e.g., primary care providers, specialty physicians, nurses, dentists, psychologists, pharmacists). A team approach, in which each healthcare provider with whom the patient has contact explores the patient’s concerns and readiness for change, is optimal.

More than 70% of the 45 million smokers in the United States report that they would like to quit, and approximately 44% of these smokers attempt to quit each year (Centers for Disease Control and Prevention, 2006). However, whereas smokers might view quitting as desirable or important, they might also lack the skills, abilities, resources, and/or coping strategies needed to feel confident in their ability to succeed. The distinction between how important it is to quit and how confident the patient is in his/her ability to quit is critical. Health care providers might erroneously assume that smokers are not concerned or do not care about the negative effects of smoking on their health when the actual barrier to quitting might actually be a patient’s lack of confidence in their ability to succeed.

A patient’s stance on smoking cessation can be quickly and easily assessed with the Importance and Confidence Rulers (Miller, 2013). After determining that the patient is a current smoker, the provider might ask a few exploratory questions:

- “What are your thoughts about quitting?”
- “What concerns you the most about continuing to smoke?”
- “What would be the benefits of quitting?”
- “On a scale from 1 to 10, with 1 being ‘not at all important’ and 10 being ‘the most important thing in your life,’ how important is it for you to stop smoking?”

With regard to the last question, the healthcare provider should follow-up on the patient’s response by asking why the patient chose that number and not a lower
number (e.g., “Why is it a seven and not a three?”). Ideally, the patient will verbalize desires, reasons, and needs for quitting, which reinforces the likelihood that the patient will quit. These questions provide a relatively quick (i.e., three to five minutes) way for the provider to clarify the patient’s knowledge and concerns about tobacco use which can then be used to tailor the rest of the discussion to the patient’s individual needs. Further, the act of verbalizing how important it is to quit is associated with increased behavioral change (Miller, 2009). Patients who report an importance level of seven or higher tend to be more motivated to make a change.

If a patient indicates an importance level of seven or higher, a few questions about how he or she would quit smoking should follow:

- “What are your thoughts about how you might quit?”
- “What resources or supports will you need to help you quit?”
- “What might get in the way?”
- “On a scale from 1 to 10, with 1 being ‘not at all confident’ and 10 being ‘completely confident,’ how confident are you that you can stop smoking?”

Once again, with regard to the last question, the health care provider should follow up on the patient’s response by asking why the patient chose that number and not a lower number. A confidence level of seven or higher is again associated with higher likelihood of making a change. Exploring these questions with patients is necessary, as patients might not be aware of many of the resources available to assist with tobacco cessation, or they may feel ambivalent about whether the resources will actually help them. Patients might benefit from receiving information from providers about effective strategies for smoking cessation, which will be addressed later in this chapter. Refer to The Five R’s – Strategies to Enhance Motivation to Quit (Table 7.1) for more detailed information about exploring importance and confidence levels.

For patients who are not ready to attempt smoking cessation, the Clinical Practice Guideline (2008) suggests making a professional recommendation that the patient quit. Approximately 5–10% of patients quit smoking based upon a clinical recommendation from their healthcare provider alone (Wilson, 1990). Some possible statements might include, “As your provider, it is important for me to tell you that quitting tobacco is the single most important thing you can do to improve your health” or “I am not sure if you realize, but quitting tobacco is the most effective treatment for COPD. It can slow the progression of the disease and improve breathlessness. I would like to help you quit whenever you are ready.”

For those who have successfully quit, screening for current use and risks for relapse remains important, as tobacco dependence is a chronic condition and may require multiple quit attempts and treatment interventions.
## Table 7.1: The Five R’s: Strategies to Enhance Motivation to Quit

<table>
<thead>
<tr>
<th>R’s</th>
<th>Motivational Factors</th>
<th>Sample Open-Ended Questions</th>
<th>Possible Patient Responses</th>
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<tbody>
<tr>
<td>Relevance</td>
<td>Importance</td>
<td>“What are your thoughts about quitting smoking?”</td>
<td>Patient offers specific personal concerns that might include:</td>
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<td>– prior quitting experiences</td>
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<td>– desires and reasons to quit</td>
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<td>– perceived ability to quit</td>
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<td>– personal barriers to cessation</td>
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<td>Risks</td>
<td>Importance</td>
<td>“What concerns you the most about continuing to smoke?”</td>
<td>Provider reflects patients concerns and may probe for concern in three specific areas:</td>
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<td></td>
<td>– Acute risks: Shortness of breath, chronic cough, respiratory infections, harm to pregnancy, impotence, infertility, loss of smell and taste.</td>
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<td>e.g., “What symptoms are you experiencing that seem related to smoking?”</td>
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<td></td>
<td>– Long-term risks: Increased risk for heart attacks, strokes, vascular disease, lung and other cancers; increased likelihood of long-term disability and need for extended care.</td>
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<td></td>
<td>e.g., “How do you think your smoking affects your COPD and overall health?”</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>– Environmental risks: Increased risk of lung cancer and heart disease in household family members; higher rates of smoking in children of tobacco users; increased risk of low birth weight, sudden infant death syndrome (SIDS), asthma, middle ear disease, and respiratory infections in children of smokers; fires.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>e.g., “What concerns you about the affect your smoking has on your family?”</td>
</tr>
</tbody>
</table>
Table 7.1: The Five R’s: Strategies to Enhance Motivation to Quit

<table>
<thead>
<tr>
<th>R’s</th>
<th>Motivational Factors</th>
<th>Sample Open-Ended Questions</th>
<th>Possible Patient Responses</th>
</tr>
</thead>
</table>
| **Rewards**    | Importance           | “What would be the benefits of quitting?” | The specific rewards identified by the patient should be reflected and emphasized several times throughout the conversation. Rewards include:  
  - Improved personal and family health  
  - Breathe more easily  
  - Food tastes better  
  - Improved sense of smell  
  - Significant financial savings  
  - Feel better about self  
  - Home, car, clothing, breath will smell better  
  - Stop worrying about quitting - free from addiction  
  - Set a good example for children  
  - Stop worrying about exposing others to smoke  
  - Feel better physically  
  - Improved performance at work and in physical activities  
  - Reduced wrinkling/aging of skin |
| **Roadblocks** | Confidence           | “What might get in the way of quitting?” | Provider could ask permission to share information about tobacco resources to address barriers. Typical barriers might include:  
  - Withdrawal symptoms  
  - Fear of failure  
  - Weight gain  
  - Managing stress  
  - Lack of support  
  - Enjoyment of Tobacco |
| **Repetition** | Importance and/or Confidence | “What are your thoughts about quitting today?” | Repeat the process at every visit for patients who continue to smoke. Reassure them that the average smoker has seven to nine quit attempts before achieving success. Offer to share strategies that will maximize their likelihood of success. |
### 7.5 Using Physiological Data When Addressing Smoking

Medical providers might use physiological data to encourage patients to consider smoking cessation. In the case of COPD, spirometry results that confirm the diagnosis and/or indicate the severity of the disease might increase patients’ concerns about smoking. Research supports the combination of providing spirometry results, supportive counseling, and nicotine replacement products to promote smoking cessation (Anthonisen, 1994; Toljamo, 2010). The manner in which a health care provider presents the information (e.g., physiological results, counseling) has a significant impact on effectiveness. Kotz and colleagues (2009) found that patients made more quit attempts but did not achieve sustained abstinence in response to health care providers who used a confrontational style to provide education about the consequences of smoking and prognosis with continued smoking.

Motivational interviewing (described later in this chapter) and the explanation of spirometry results in terms of “lung age” improve abstinence rates (Parkes, 2008). “Lung age” is the translation of FEV₁ values into a concept that is easier for patients to understand and internalize. Providing information about “lung age,” or the age that the lungs would appear to be if the spirometry test had been completed on a healthy person who never smoked, demonstrates premature aging in the lungs that is caused by smoking and/or other environmental irritants. For example, telling a 55-year-old smoker that his lung function is comparable to that of a 95-year-old who has never smoked might be more meaningful and effective than telling him that his FEV₁ is 77% of predicted. (See Chapter 4, Pulmonary Function Testing: Spirometry: Presence and Severity of Airflow Limitation/Obstruction for more information.)

Researchers have identified specific populations who seem to benefit from receiving spirometry results as part of the smoking cessation intervention. Patients who are diagnosed with moderate to severe airflow obstruction experience more success with smoking cessation when spirometry results are provided (Gorecka, 2003). Additionally, patients who are motivated to quit, are receiving pharmacotherapy, are of older age, and have a higher body mass index demonstrate more success with tobacco cessation when spirometry results are provided (Toljamo, 2010).

### 7.6 How to Present Spirometry Results to Promote Smoking Cessation

Motivational interviewing (MI), a collaborative approach that elicits patients’ reasons for change, offers an effective strategy when sharing spirometry results with patients. In keeping with the patient-focused spirit of MI, it is critical to ask for the patient’s permission before providing information. Asking the patient before sharing results demonstrates respect for the patient’s autonomy and the patient’s ability to choose whether he/she wants to hear the information. After gaining permission to
Table 7.2: A Sample Conversation Between a Provider and a Patient Illustrating the Four-Step Ask–Elicit–Tell–Elicit Process

<table>
<thead>
<tr>
<th>Step</th>
<th>Role</th>
<th>Sample Conversation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ask</td>
<td>Provider</td>
<td>“I would like to go over your spirometry results with you today. Is that okay?”</td>
</tr>
<tr>
<td></td>
<td>Patient</td>
<td>“Sure.”</td>
</tr>
<tr>
<td>Elicit</td>
<td>Provider</td>
<td>“First, can you tell me what you already know about the lung function test?”</td>
</tr>
<tr>
<td></td>
<td>Patient</td>
<td>“Well, I guess it will say whether I have lung disease or not.”</td>
</tr>
<tr>
<td>Tell</td>
<td>Provider</td>
<td>“Yes, that’s right. Actually, it helps me determine if you have a lung disease, how severe it is, and to some extent, what type of lung disease. Your results show that you have moderate airflow obstruction characteristic of Chronic Obstructive Pulmonary Disease. To help you understand how your lungs are doing, I’ve calculated your lung age. Lung age is the age your lungs appear to be if you were a healthy person who never smoked. So, even though you are 55, your lungs are functioning like a 95-year-old. What do you make of that?”</td>
</tr>
<tr>
<td></td>
<td>Patient</td>
<td>“Are you kidding? Is there anything I can do to reverse it?”</td>
</tr>
<tr>
<td>Elicit</td>
<td>Provider</td>
<td>“The most important thing you can do to preserve your lung function is to stop smoking. I would like to talk to more about that, but, first, can you tell me what you think it means to have the lung age of a 95-year-old?”</td>
</tr>
<tr>
<td></td>
<td>Patient</td>
<td>“I guess it means that smoking has aged my lungs by about 40 years!”</td>
</tr>
</tbody>
</table>

discuss spirometry results, a four-step process of Ask–Elicit–Tell–Elicit is recommended. Table 7.2 depicts each step in a sample conversation between a provider and patient.

The Ask–Elicit–Tell–Elicit sequence supports patient autonomy by offering a small amount of information in easy-to-understand terms and then probing for the patient’s reaction and understanding. It is essential that the provider seeks the patient’s reaction without imposing his/her own opinions so that the patient will feel free to articulate his/her experience and concerns.

### 7.7 Readiness for Change

The Transtheoretical Model of Change (Prochaska, 1983) is a theoretical model of behavior change that was originally drafted by examining the attributes and strategies of self-changers who successfully quit smoking without professional assistance. This temporal model is based on the assumption that behavior change is not a discrete event, but rather a process that occurs in stages across time. Rather than
assuming that the decision to quit smoking happens on one specific day, the model acknowledges that people are more likely to go through an extended process that may include the following: spend a few months questioning whether to quit or not, seek help from a PCP, weigh the pros and cons for another month, set a quit date, buy nicotine replacement products, change daily routines, seek support from a friend, stop smoking on the quit date, call a telephone quit line for support, relapse after two weeks, seek additional support, etc.

According to this model, there are five stages through which people progress, often in a non-linear fashion. In general, a person moves from being uninterested, unaware, or unwilling to make a change (precontemplation), to considering a change (contemplation), to deciding and preparing to make a change (preparation), to taking steps and problem-solving challenges or barriers (action), to incorporating the change into a daily routine (maintenance). Relapses are almost inevitable and become part of the process of working toward permanent change. The following descriptions of each stage were adapted from Velicer and colleagues (1998):

7.7.1 Precontemplation

Precontemplation, the initial stage, is characterized by people who have no intention of quitting in the next six months. Smokers in this stage are likely to deny that smoking causes any problems in their lives. Patients in this stage are uninformed or underinformed. When information is presented, they may try to avoid or deny it. People in this stage might have tried to change and failed, leaving them feeling hopeless and demoralized. Tobacco treatment programs are often not designed for people in the precontemplation stage. It is estimated that 40% of current smokers are in the precontemplation stage (Velicer, 1995).

Clinician Goals During the Precontemplation Stage:
1. Validate the patient’s experience.
2. Encourage further self-exploration through smoking self-assessment tools (e.g., Fagerstrom Test for Nicotine Dependence (Heatherton, 1991)).
4. Offer websites where patients can go to learn more (e.g., www.smokefree.gov).
5. Leave the door open for future conversations.

Open-Ended Questions to Facilitate Change During the Precontemplation Stage:
1. “What would have to happen to let you know that smoking is a problem?”
2. “What warning signs would let you know that smoking is a problem?”
3. “Tell me about times when you have tried to quit in the past.”
4. “How might smoking cause problems for you in the future?”
5. “If you do nothing to change the way you take care of your health, what is the worst thing that might happen in 10 years?”

### 7.7.2 Contemplation

Contemplation, the second stage, is characterized by patients who intend to change in the next six months. They are more likely to acknowledge that smoking is a problem and consider reasons for quitting. Unresolved ambivalence is a hallmark of this stage, as patients consider the costs and benefits of continuing to smoke. The importance of quitting might rise, but a lack of confidence and a fear of failure interferes with quit attempts. Patients who are attempting to stop smoking spend an average of two years in contemplation, searching for a feasible, simple, quick solution. They are often not ready for traditional, action-oriented programs. Forty percent of current smokers tend to be in the contemplation stage.

**Clinician Goals During the Contemplation Stage:**
1. Validate the patient’s experience.
2. Explore the patient’s perceptions of the barriers and benefits of quitting smoking.
3. Help the patient clarify values that are inconsistent with smoking, such as being a good role model for children.
4. Encourage further self-exploration through smoking self-assessment tools (Fagerstrom Test for Nicotine Dependence (Heatherton, 1991)).
5. Offer factual written information about the risks of smoking and the benefits of quitting.
6. Educate about the resources available and their efficacy, including nicotine replacement treatments (NRTs), medications, quit lines, text support, mobile apps.
7. Leave the door open for moving to preparation.

**Open-Ended Questions to Facilitate Change During Contemplation Stage:**
1. “Why do you want to stop smoking now?”
2. “What are the reasons for not quitting?”
3. “What concerns you the most about your smoking?”
4. “What might keep you from quitting right now?”
5. “What might help you overcome the barriers to quitting?”
6. “What people, programs or behaviors might help you quit?”
7. “What do you think you need to learn about the effects of smoking or how to quit?”
7.7.3 Preparation

Preparation, the third stage, occurs when patients plan to make a behavioral change in the next month. They have taken steps to prepare, like researching tools and programs that they might use to quit. Ambivalence may still be present, but the pros tend to outweigh the cons. Patients in the preparation stage may spend a considerable amount of time thinking about and planning the strategies they will use. Small steps leading toward behavior change might be attempted (e.g., cutting back on the number of cigarettes smoked, making their intentions to quit public). These patients are ready for traditional tobacco treatment programs and are likely to follow through with treatment. About 20% of current smokers are in the preparation stage.

Clinician Goals During the Preparation Stage:
1. Praise the decision to change behavior.
2. Offer a variety of resources to quit, including NRTs, medications, tobacco treatment groups, quit lines, text support, and mobile apps.
3. Identify and assist in problem-solving obstacles.
4. Encourage small initial steps.
5. Encourage identification of social supports.

Open-Ended Questions to Facilitate Change During the Preparation Stage:
1. (Pick one of the patient’s barriers to quitting) “What are some things you could do to overcome this barrier?”
2. “What additional steps can you take to feel certain that you will succeed?”
3. “How will you feel about yourself when you are able to quit for good?”
4. “Who will support you in your first few months of quitting?”
5. “How will you change your environment to help you quit?”
6. “What will you do to distract yourself when you have a craving?”

7.7.4 Action

Action involves an actual smoking cessation attempt and includes the first six months after quitting. Patients in the action stage move from thinking and planning to doing. The strategies used in the action stage involve stimulus control, substitution, and rewards. Behaviors that support stimulus control include disposing of cigarettes and paraphernalia (e.g., lighters, ash trays) before the quit date, avoiding the gas station or other location where cigarettes were typically purchased, and choosing not to drink alcohol during the first three months of quitting (because of the strong association between smoking and consuming alcohol). Behaviors that support substitution involve planning an alternate activity or action to replace smoking or smoking related behaviors. Patients might drink water or use a nicotine replacement therapy when a craving arises. Some patients substitute a cinnamon stick or flavored toothpick for a cigarette
to satisfy the familiar hand-to-mouth action that is involved in smoking. Rewards that are obtained during this stage can be internal or external. Positive self-statements and a sense of accomplishment and pride can offer powerful reinforcement. Tangible rewards, such as using the money saved from cigarettes to invest in a desired item or activity, are concrete benefits of quitting. Recognition of positive changes from other members and providers in a tobacco treatment program can also be reinforcing.

Clinician Goals During the Action Stage:
1. Affirm steps to change.
2. Explore and highlight successful strategies and benefits.
3. Probe for cravings and struggles, and problem-solve ways to manage them.
4. Encourage continued use of a variety of support options, including NRTs, medications, tobacco treatment groups, quit lines, text support, and mobile apps.

Open-Ended Questions to Facilitate Change During the Action Stage:
5. “What has worked in taking this step?”
6. “What could help it work even better?”
7. “What else would help?”
8. “How do you reward yourself for not smoking?”
9. “How committed are you to remaining a non-smoker?”

7.7.5 Maintenance

Maintenance generally begins six months after quitting and can last indefinitely. Cravings tend to dwindle for most patients and less vigilance and effort is required to remain smoke-free. However, relapse is common during this stage. The average smoker makes seven to nine quit attempts before becoming fully successful. The most frequently cited reason for relapse is the emersion of an emotional stressor. The patient in the maintenance stage should be encouraged to consider and plan for how he or she might manage stressful situations without resuming smoking. Weight gain is a second reason people (particularly women) cite for a relapse. It is important for the patient to incorporate healthy strategies that will address managing both emotional stressors and cravings during the maintenance stage. Examples of these strategies include using nicotine replacement therapies, participating in exercise, and engaging in relaxation. While relapse potential is high (95% in some samples), research suggests that the majority of smokers who relapse (85%) do not return to the beginning of the change process (i.e., the precontemplation stage) (Prochaska, 2006). Rather, patients are much more likely to return to the contemplation stage.

Clinician Goals During Maintenance Stage:
1. Praise continued success.
2. Review and highlight successful strategies and benefits.
3. Explore risks for relapse and problem-solve ways to manage them.
Open-Ended Questions to Facilitate Change During the Maintenance Stage:
4. “Congratulations! What’s helping you?”
5. “What else will help?”
6. “What are your high risk situations and how do you prepare for them?”
7. “What is the best part about being a non-smoker?”

7.8 The 5 A’s Model

The 2008 Clinical Practice Guideline (U.S. Department of Health and Human Services) recommend providers use a five-step process (Ask, Advise, Assess, Assist, Arrange) for identifying current smokers and assisting them in quitting.

7.8.1 Step 1: ASK

The best practice for identifying current tobacco users is to ask every patient about his or her smoking habits at every visit. Some may view this approach as “badgering” the patient. However, assessing smoking habits at every visit can have a significant impact across time if the questions are asked in a non-judgmental way that takes into account the patient’s readiness to change. System changes can be used to standardize this approach by implementing a reminder system within an electronic medical record or incorporating tobacco screening in the collection of vitals, although the effectiveness of reminders systems has been mixed. A review of seven randomized control trials found that reminder systems alone increased the number of patients advised to quit by 13% and the patients who were successful in quitting by 4% (Zaza, 2005). However, the Clinical Practice Guideline (2008) reviewed three studies and found that reminder systems did not have a significant impact on smoking cessation rates. Reminders sometimes prompt health care professionals to address smoking cessation in an ineffective way (e.g., “You meet this criteria. Do you want this service?”). While asking is an important first step, evidenced-based approaches should then be used to motivate and prepare smokers to quit. Caplan and colleagues (2011) indicate that two-thirds of patients are asked about smoking status, yet only about 20% of those identified as smokers are offered support for quitting. As such, appropriate clinical follow-up with strategies discussed in this chapter should also be used to improve the effectiveness of these systems.
7.8.2 Step 2: ADVISE

As reviewed earlier in this chapter, a personalized statement recommending that the patient consider quitting can have an impact on those who are ambivalent. Including a message of support and assistance can help to create a sense of collaboration.

7.8.3 Step 3: ASSESS

Assess whether current smokers are ready to quit. Use open-ended questions to explore readiness for change. Use the importance and confidence rulers (Table 7.1) to gauge investment and potential barriers. See the Screening and Readiness for Change sections earlier in this chapter for more specific strategies.

7.8.4 Step 4: ASSIST

Assist patients who are willing to quit by offering nicotine replacement therapy (NRT), medications, and more intensive services. Offer the full array of options available and allow the patients to select the ones that suit them the best. Share information about success rates for each form of treatment and the most effective combinations of treatments. Honor whatever choice they select without judgment. Specific options and more detailed information about NRTs and medication will be discussed in the Interventions section of this chapter.

Patients who elect to take NRTs or medication without additional services, as well as those who decline to receive any services, should be invited to consider some strategies to help them prepare to quit, if they are ready to do so. Written patient education materials can be useful and effective, especially fill-in-the-blank-style handouts that patients can use to personalize their quit plans (see Figure 7.2 for an example; “Tobacco Cessation: How to Change?” Handout (Altum, 2013)). Table 7.3 identifies key ingredients of a quit plan to review when a patient decides to quit. Table 7.4 lists potential barriers to quitting, triggers for smoking, and strategies that patients can use to overcome these challenges (Himstreet, 2013).

7.8.5 Step 5: ARRANGE

Ideally, the provider or a nurse on the Primary Care team offers follow-up either in-person or by phone. Secure email may be another option. Clinical Practice Guideline (2008) recommend contact at one week and one month after the quit date. Issues to address in the follow-up contacts include:
Tobacco Cessation: How to Change?

Do you want to change your tobacco use? If you answer yes, the best way is to take into account all the factors that contribute to your use. It can help to think of these factors as falling into one of these 3 main groups:

- Physical Factors
- Behavioral Factors (habits)
- Psychological Factors (feelings)

Physical Factors
Nicotine is the most addictive substance on the planet. But, there is help. Your doctor will help you decide if you can use a nicotine replacement product, such as the patch or gum. These products are shown to help people quit and are often the key to success.

- Most often there is a better success rate when a medication type of product is used.
- Some medications, like Zyban, are very helpful to some people. But for others, they don’t seem to offer enough help with nicotine cravings.
- For some people, using two types of products will work better to relieve cravings and withdrawal symptoms than just using one.

Work closely with your doctor to find the best replacement product(s) for you.

Behavioral Factors
You need to change your habits and the situations where you most often use tobacco. There are some times when you have greater cravings for tobacco. Counseling and support are helpful to those trying to quit. You can learn skills to help you make other choices at these times.

- Be more aware of the situations when you are most tempted to use nicotine
- Learn problem-solving skills to better cope with these situations

What does the VA offer to help?
- Tobacco cessation groups/classes
- Individual counseling through tobacco cessation clinics.

If you would find telephone counseling helpful, you can call 1-800-QUIT-NOW (1-800-784-8669). You will be connected to your state’s phone support staff.

Behavioral Factors
Your feelings (thoughts and emotions) are some of the hardest aspects of tobacco use to change. Often, people think that they need tobacco to get through their tough times. Changing these thoughts to cope with stress is a vital aspect of beating this habit.

One helpful strategy is to list your top 3 reasons for quitting, and remind yourself of them as a way to stay strong if you need a boost along the way. Take a moment to list your main reasons for quitting:

1. 
2. 
3. 

Figure 7.2: How to Change Handout. This How to Change Handout for Smoking Cessation uses the 5 A’s Approach: Avoid, Alter, Alternatives, Action, and Appointment to assist providers in helping their patients stop smoking.
Preparing to Quit

Your Quit Date

When is the last day and time that you are going to use tobacco?

Month______ Day______ Year______ Time_____

Prepare Your Surroundings

What are the things that remind you to use tobacco? It is important to change these things so you won’t be reminded about tobacco use as often.

Before your quit date consider the following:

• Don’t buy tobacco in bulk (e.g., don’t buy cartons).

• Find all of your hidden stashes of tobacco. Check in the couch, the car, in your drawers at home and at work. It is unwise to keep an emergency stash once you quit.

• Get rid of tobacco-related materials—things like ashtrays and lighters. Don’t carry lighters or matches in your pockets or purse.

• Prepare family and friends. Let them know that you are planning to quit. Ask for their help. If you have friends and family who do use tobacco, ask them to avoid using it around you.

• Prepare a plan for to cope with your cravings and withdrawal symptoms. Use the combination of strategies that works for you.

• Choose a method to quit. There are many ways to think about quitting. But one of the most important considerations is to avoid thinking favorably about your last tobacco use. If you remember your tobacco fondly, then you are more likely to go back to using it when you think you need it.

Quitting is difficult. Many people feel it’s a challenge. Preparing for difficult situations as you quit can help you succeed. What do you expect to be the hardest challenge for you as you quit?

○ Will it be going without a cigarette with your morning coffee?

○ Will it be not smoking when your spouse or friends light up?

Anticipating and having a plan for how to handle these challenges will increase your success.

As you prepare to quit there are other things in your life that you can change that will help you to be successful. Think about the places you should avoid or things you should do differently.

• Avoid: What situations (e.g., bars, sporting events, smoking areas) do you need to avoid during the next month to limit your urges to use tobacco?

• Alter: How can you change situations that you can’t avoid so that you’ll be more successful with your quit attempt?

• Alternatives: “When you feel the urge to put tobacco in your mouth what could you use instead” (e.g., gum, hard candies or mints, toothpicks, cinnamon sticks)?

• Activities: “Are there things you can do (e.g., going for a walk) or ways to keep you busy if you feel an urge to use tobacco?”

continued Figure 7.2: How to Change Handout. This How to Change Handout for Smoking Cessation uses the 5 A’s Approach: Avoid, Alter, Alternatives, Action, and Appointment to assist providers in helping their patients stop smoking.
Using the Four A’s to Outsmart Tobacco Urges

**Avoid.** What are the situations or places that you need to avoid over the next month?
1. 
2. 
3. 

**After.** What situations will you need to change to help you be more successful?
1. 
2. 
3. 

**Alternatives.** What can you put in your mouth or hands instead of using tobacco?
1. 
2. 
3. 

**Action.** When you get an urge to use tobacco, what can you do to be active or busy?
1. 
2. 
3. 

**Follow-Up Appointment Plan:**

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continued Figure 7.2: How to Change Handout. This How to Change Handout for Smoking Cessation uses the 5 A's Approach: Avoid, Alter, Alternatives, Action, and Appointment to assist providers in helping their patients stop smoking.
Table 7.3: Key Elements of a Quit Plan

- Set a quit date. Some time to prepare is often indicated but long delays may preclude action.
- Share the quit plan with others and ask for their understanding and support.
- Identify potential challenges and triggers and how they will be overcome. These might include withdrawal symptoms, daily routines that are heavily associated with smoking, alternative strategies for coping with stress and cravings, etc. Each patient may have a different perspective of challenges. It may be useful to offer a list (see Tab. 7.4) and ask them to select the top three or four items to address.
- Remove tobacco products from home, work, and car.
- Consider making the home smoke-free.
- Identify and plan for challenging triggers by altering or avoiding them (e.g., avoid spending time with others who smoke, go for a walk in the morning instead of smoking a cigarette and taking a shower first thing).
- Consider avoiding alcohol because alcohol use is associated with tobacco relapse.
- Offer information about additional supports such as telephone quit lines, text support, mobile apps, and websites.
- Have tobacco treatment education materials in every exam room to offer when patients are preparing to quit.

1. Congratulating them if they remain abstinent. Probing for strategies that have led to their success.
2. Exploring medication use and side effects.
3. Problem-solving ways to address any slips or challenges to managing cravings.
4. Asking about use of additional supports and reviewing available resources as needed.
5. Plan to review again at the next clinic visit.

7.9 Motivational Interviewing

Motivational Interviewing (MI) is an evidenced-based interviewing style that seeks to draw out a patient’s own reasons for change. MI is a collaborative approach that recognizes and supports the patient’s struggles, values, beliefs, and desires. Skilled clinicians move the interview towards change while respecting the patient’s autonomy and personal choice.
Table 7.4: Barriers to Quitting, Triggers for Smoking, and Strategies to Overcome Both Barriers and Triggers

<table>
<thead>
<tr>
<th>Barriers</th>
<th>I have not been able to quit in the past.</th>
<th>I do not know what to do without a cigarette.</th>
<th>I am afraid it will make my stress, anxiety, or mood worse.</th>
</tr>
</thead>
<tbody>
<tr>
<td>I live with others who still smoke.</td>
<td>How will I socialize with my friends who still smoke?</td>
<td>I cannot get back to sleep unless I smoke a cigarette.</td>
<td></td>
</tr>
<tr>
<td>I am concerned about weight gain.</td>
<td>I am worried about how I will handle stress.</td>
<td>It is the only vice I have left; I quit everything else.</td>
<td></td>
</tr>
<tr>
<td>I smoke when I am bored.</td>
<td>I always have a cigarette with my coffee/beer.</td>
<td>I do not know how to say “no.”</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Triggers</th>
<th>Waking up in the morning</th>
<th>Drinking coffee</th>
<th>Stress</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before bedtime</td>
<td>Drinking alcohol</td>
<td>After meals</td>
<td></td>
</tr>
<tr>
<td>Driving</td>
<td>After sex</td>
<td>During breaks</td>
<td></td>
</tr>
<tr>
<td>Working on the computer</td>
<td>Talking on the phone</td>
<td>Waking during the night</td>
<td></td>
</tr>
<tr>
<td>Feeling bored</td>
<td>After completing a task</td>
<td>Having nightmares</td>
<td></td>
</tr>
<tr>
<td>Feeling anxious, angry, impatient</td>
<td>Seeing and/or smelling someone else smoke</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Behavioral Strategies</th>
<th>Avoid stressful situations whenever possible.</th>
<th>Remove triggers (e.g., ashtrays, lighters) from home, car, clothing, etc.</th>
<th>Exercise. Go for a walk.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fill your time with enjoyable hobbies and interests that are not associated with tobacco use.</td>
<td>Stock up on tobacco substitutes (e.g., sugar-free chewing gum and candy, carrot and celery sticks, toothpicks, straws, cinnamon sticks).</td>
<td>Keep track of the number of cigarettes smoked to make the behavior less automatic.</td>
<td></td>
</tr>
<tr>
<td>Practice relaxation techniques (e.g., deep breathing exercises).</td>
<td>Move your tobacco to a different location that is less convenient to access.</td>
<td>Wait to smoke after waking, eating, etc. Slowly increase the amount of time daily - wait 10 minutes today, 20 minutes tomorrow, etc.</td>
<td></td>
</tr>
<tr>
<td>Brush your teeth.</td>
<td>Talk to a friend or family member. Do a crossword puzzle or Sudoku.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
7.9.1 Clinical Effectiveness of Motivational Interviewing for Treating Tobacco Use Disorder

A randomized, controlled trial conducted in Spain found that three 20-minute physician interventions using MI were five times more effective than three minutes of advice and guidance to quit smoking offered by the same physician (Raim undo, 2006). In a review of four meta-analyses of the clinical effectiveness of MI for tobacco cessation, Lundahl and Burke (2009) found that MI success rates ranged from 5% to 17% above no treatment at all, with mixed findings when MI was compared with other evidence-based treatments. Ideally, MI should be incorporated into a package of treatment approaches that complement one another. This interviewing skill might be most effective in Primary Care or Pulmonary Specialty Care clinics, where patients are most likely to be in the precontemplation or contemplation stages of change. Denial and ambivalence are prominent features of these stages, and MI strategies are well-suited to promoting movement and investment in change.

7.9.2 Developing Competency in the Use of Motivational Interviewing

There are currently no established standards for developing competency in MI. However, MI experts tend to agree that 14 to 28 hours of training followed by audio-taped practice and supervision are generally needed to achieve proficiency in several critical and quantifiable skill domains. Efraimsson and colleagues (2011) addressed the question of whether four days of MI training impacted nurses’ use of MI communication for smoking cessation with COPD patients. The nurses’ interventions were more instructive (e.g., provided information, closed questions, simple reflections) and rarely expressed empathy using complex reflections, collaborated with patients, or supported the patients’ choices, thereby making them less likely to support motivation for change. This study suggests that follow-up practice and supervision are necessary to gain proficiency in MI. The authors propose that training in MI needs to be integrated into nursing education, at the basic and advanced levels, with audio- or video-taped supervision needed to achieve proficiency. Annual training and proficiency evaluations would ensure competence is maintained. These recommendations would be advisable for all healthcare professions who address health behavior change, such as physicians, nurses, dieticians, clinical pharmacists, social workers, psychologists, physical and occupational therapists, and speech pathologists.

7.10 Interventions

Smoking cessation intervention options that are provided to patients should be numerous and varied. Patients should be encouraged to use multiple strategies rather
Interventions

than selecting only one at a time. Tobacco treatment options might include group or individual counseling (in outpatient mental health or in specialty medical clinics), nicotine replacement therapy (NRT), medications (e.g., bupropion [Wellbutrin] or varenicline [Chantix®]), telephone quit lines, home telehealth programs, Nicotine Anonymous, mobile apps, websites and text support. Daily support strategies like home telehealth, a daily home monitoring system, or a mobile app with daily log-in, can support the frequency of cravings in the first month of quitting. Telephone quit lines might be especially useful in the maintenance stage, when there is a higher likelihood of emotional stressors that may lead to relapse.

Brief interventions (3–10 minutes) for smoking cessation that occur in the Primary Care setting have been associated with smoking cessation rates of 5–10% (Wilson, 1990). More intense interventions lead to a greater likelihood of success. Interventions can be made more intense by increasing the number of sessions, the length of the sessions, or the follow-up period. Having at least 4 individual brief (10–15 minute) appointments substantially improves abstinence rates (2–3 sessions: 16%; 4–8 sessions: 21%; Clinical Practice Guidelines, 2008). Additionally, a multidisciplinary team approach in a primary care setting might allow for more frequent review of the patient’s efforts to quit.

In general, studies of successful tobacco treatment confirm that a structured counseling program combined with an NRT and/or medication is the most successful (see Table 7.4). This result was replicated in a review of randomized controlled clinical trials of tobacco treatment for COPD patients (Parker, 2012). Table 7.5 identifies success rates by type of intervention.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Success Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Counseling + NRT/medication</td>
<td>22% – 32%*</td>
</tr>
<tr>
<td>Medication alone</td>
<td>24% – 33%*</td>
</tr>
<tr>
<td>NRT’s alone</td>
<td>19% – 27%*</td>
</tr>
<tr>
<td>Counselling alone</td>
<td>12% – 25%*</td>
</tr>
<tr>
<td>Brief interventions in Primary Care</td>
<td>8% – 12%*</td>
</tr>
<tr>
<td>Self-Initiated Strategies</td>
<td>8% – 10%*</td>
</tr>
</tbody>
</table>

* consolidated data from 2008 Clinical Practice Guidelines
7.10.1 Nicotine Replacement Therapies and Medications

As indicated, nicotine replacement therapies and medications – either used individually or in combination with counseling – lead to the highest cessation rates. Nicotine replacement therapies and medications are considered to be critical for any patient who wants to quit smoking and should be offered to everyone engaging in smoking cessation. If a patient is not having success with smoking cessation while using a particular NRT or medication regimen, the provider should adjust the types and/or dosages of NRTs and/or medications, or try a combination of therapies (Ebbert, 2007). Nicotine cravings and unmanageable withdrawal symptoms are common reasons for relapse when NRT’s or medications are not used or used in insufficient dosages. Burke et al. (2008) suggested monotherapy with an NRT for patients who smoke 10 cigarettes per day or less. Relapse after monotherapy usually suggests the need to add additional agents. Patients who smoke more than 10 cigarettes per day are encouraged to try a combination of NRTs; this might include wearing a nicotine patch that provides steady dosing, and choosing nicotine gum, spray, lozenge, or inhaler for breakthrough cravings or withdrawal symptoms. The researchers note that while the FDA has not approved combination therapy, their evidence supports the practice of NRT combination therapy.

Tobacco treatment literature describes tobacco dependence as a chronic condition, and, as such, the effectiveness and the type and dosage of the NRT and/or medication needs to be regularly evaluated. Recommendations and doses for NRTs and tobacco cessation medications should be adjusted with each quit attempt, much the same way medications and doses are adjusted over time for hypertension or diabetes (Burke, 2008). Table 7.6 offers a summary of NRT’s and medications for tobacco dependence. See medication package inserts for complete information.

Unfortunately, only 22% of smokers who attempt smoking cessation use a nicotine replacement product or medication (Clinical Practice Guideline, 2008). Additionally, many smokers have unrealistic expectations about the quitting process and stop using NRTs or medications prematurely, which leads to relapse. Discussing these misconceptions and sharing information about the most effective smoking cessation strategies might help patients succeed.

7.11 Other Nicotine Sources

Although outside of the scope of this chapter, smokeless tobacco (e.g., chewing tobacco, snuff, and dissolvable tobacco) also has deleterious effects. While smokeless tobacco does not directly cause or contribute to symptoms of COPD, it has been shown to cause a variety of negative health effects, including mouth, tongue, cheek, gum and throat cancer, esophagus cancer, stomach cancer, and pancreatic cancer (American Cancer Society, 2013). Additionally, while smokeless tobacco products are
### Table 7.6: Pharmacologic Treatments for Smoking Cessation

<table>
<thead>
<tr>
<th>Medication</th>
<th>Features</th>
<th>Dosing</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine Patch</td>
<td>– OTC</td>
<td>For &lt;10 cigarettes/day:</td>
<td>– Skin irritation</td>
</tr>
<tr>
<td></td>
<td>– 24 hour delivery</td>
<td>– 14 mg for 6 wks</td>
<td>– Sleep disturbance or vivid dreams</td>
</tr>
<tr>
<td></td>
<td>– Slow to build up</td>
<td>– 7 mg for 2 wks</td>
<td>– Require additional adhesive with sweating</td>
</tr>
<tr>
<td></td>
<td>– Rotate patch site; anywhere on the upper body</td>
<td>For &gt;10 cigarettes/day:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>– 21 mg for 4–6 wks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>– 14 mg for 2–4 wks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>– 7 mg for 2–4 wks</td>
<td></td>
</tr>
<tr>
<td>Nicotine Gum</td>
<td>– OTC</td>
<td>&lt;20 cigarettes/day:</td>
<td>– Improper “chewing” leads to less nicotine absorbed &amp; stomach upset</td>
</tr>
<tr>
<td></td>
<td>– Delivers nicotine through the mouth while gum is parked between cheek and gum</td>
<td>– 2 mg gum</td>
<td>– Mouth soreness</td>
</tr>
<tr>
<td></td>
<td>– Quick delivery</td>
<td>&gt;20 cigarettes/day:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Avoid eating or drinking 15 min before or during use</td>
<td>– 4 mg gum</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Chew 15–30 times then park between cheek and gum until tingle fades</td>
<td>Dosing:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>– 1–2 pieces per 1–2 hrs for 6 wks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>– 1 piece per 2–4 hrs for 3 wks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>– 1 piece per 4–8 hrs for 3 weeks</td>
<td></td>
</tr>
<tr>
<td>Nicotine Lozenge</td>
<td>– OTC</td>
<td>&lt; 20 cigarettes/day:</td>
<td>– Throat irritation</td>
</tr>
<tr>
<td></td>
<td>– Delivers nicotine through the mouth while lozenge dissolves; 25% more nicotine than gum</td>
<td>– 2 mg</td>
<td>– Nausea (12–15%)</td>
</tr>
<tr>
<td></td>
<td>– Quick delivery</td>
<td>&gt; 20 cigarettes/day:</td>
<td>– Hiccups</td>
</tr>
<tr>
<td></td>
<td>– Avoid eating or drinking 15 min before or during use</td>
<td>– 4 mg</td>
<td>– Heartburn</td>
</tr>
<tr>
<td></td>
<td>– Should not be chewed or swallowed</td>
<td>Dosing:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>– 1–2 pieces per 1–2 hrs for 6 wks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>– 1 piece per 2–4 hrs for 3 wks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>– 1 piece per 4–8 hrs for 3 weeks</td>
<td></td>
</tr>
<tr>
<td>Nicotine Nasal Spray</td>
<td>– Prescription only</td>
<td>1 spray in each nostril</td>
<td>– Nose and eye irritation in 1st week especially</td>
</tr>
<tr>
<td></td>
<td>– Delivers nicotine through the oral mucosa but is NOT sniffed</td>
<td>1–2x/hr</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Fastest NRT delivery system</td>
<td>Average 14–15 doses/day initially; 40 doses/day max</td>
<td></td>
</tr>
<tr>
<td>Nicotine Inhaler</td>
<td>– Prescription only</td>
<td>Minimum 6 cartridges/day; Max 16/day</td>
<td>– Few reported</td>
</tr>
<tr>
<td></td>
<td>– Delivers nicotine through the mouth</td>
<td>– Each cartridge designed for 80 puffs in 20 min.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Quick delivery; need to puff more frequently than a cigarette</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
less lethal than cigarettes, they are not recommended as a cigarette substitute as they have not been proven to help smokers quit.

The electronic cigarette (e-cigarette) has become another popular nicotine delivery system. Research about the e-cigarette’s potential negative health effects is still sparse. Questions about the safety of inhaling the substances found in e-cigarettes into the lungs have been raised (The American Cancer Society, 2014). The limited available research indicates that e-cigarettes cause short-term lung changes. The long-term effects are still unclear. Additionally, the ingredients in e-cigarettes are not identified, making the substances and nicotine levels contained within them unclear. As the safety and effectiveness of e-cigarettes is currently unknown, The American Cancer Society indicates that they cannot recommend the e-cigarette as a nicotine replacement therapy. With regard to both smokeless tobacco and the e-cigarette, it is important to discuss the potentially harmful health effects that these tobacco and nicotine products can cause.

### Table 7.6: Pharmacologic Treatments for Smoking Cessation

<table>
<thead>
<tr>
<th>Medication</th>
<th>Features</th>
<th>Dosing</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupropion SR</td>
<td>Non-nicotine prescription</td>
<td>150 mg 1x/day for 3 days</td>
<td>Increased risk of seizures (1:1000)</td>
</tr>
<tr>
<td>(Wellbutrin®)</td>
<td>May be used in combination with NRT’s</td>
<td>150 mg BID for 4 days before quit date</td>
<td>Insomnia (daytime dosing suggested, 8 hours apart)</td>
</tr>
<tr>
<td></td>
<td>Start 1 week before quit date</td>
<td>Continue 150 mg BID for 8 wks – 6 mo.</td>
<td>Use with caution in patients with liver disease</td>
</tr>
<tr>
<td></td>
<td>Beneficial for smokers with depression</td>
<td></td>
<td>Dry mouth</td>
</tr>
<tr>
<td>Varenicline</td>
<td>Non-nicotine prescription</td>
<td>0.5 mg 1x/day for 3 days</td>
<td>Nausea, take with food</td>
</tr>
<tr>
<td>(Chantix®)</td>
<td>Not recommended with NRT’s</td>
<td>0.5 mg BID for 4 days</td>
<td>Adjust dose if kidney function is impaired</td>
</tr>
<tr>
<td></td>
<td>Start 1 week before quit date</td>
<td>1.0 mg BID for 11 weeks</td>
<td>Monitor for irritability and suicidality</td>
</tr>
<tr>
<td></td>
<td>May stop abruptly without taper</td>
<td>May continue up to 24 weeks total</td>
<td>Avoid use with serious psychiatric illness</td>
</tr>
</tbody>
</table>
7.12 Conclusion

Eighty to 90% percent of patients diagnosed with COPD are current or past smokers. Thus, the single most important approach to treating and preventing COPD is smoking cessation.

More than 70% of the 45 million smokers in the United States report that they would like to quit, and approximately 44% of those people attempt to quit each year. NRT’s and medications – either used individually or in combination with counseling – lead to the highest cessation rates. Unfortunately, only 22% of smokers who attempt smoking cessation use a nicotine replacement product or medication. Smokers should be offered multiple resources to help them quit and be encouraged to use more than one. The role of Primary Care in tobacco treatment is to (1) assess the patient’s readiness for change, (2) match the intervention strategy to the patient’s stage of change, (3) ask open-ended questions that explore the risks, roadblocks, rewards, and relevance of quitting, and (4) use the five A’s process: Ask about smoking status at every visit; Advise smokers to quit; Assess readiness for change; Assist patients with a variety of resources; and Arrange follow-up.

7.13 Summary Points

1. Up to 90% of those diagnosed with COPD are or were smokers; therefore, addressing smoking cessation is important to prevent and treat COPD.
2. Abstinence from tobacco is associated with a variety of health improvements, including decreased mortality and reduced risk of developing lung cancer, myocardial infarction, and stroke.
3. Providers should screen patients for tobacco use at each visit; Providers can use the five A’s process (Ask about smoking status at every visit; Advise smokers to quit; Assess readiness for change; Assist patients with a variety of resources; and Arrange follow-up).
4. Providers can use a variety of data to encourage patients to consider and follow through with smoking cessation, including lung age to explore the patient’s perceived need to quit and statistics about effective treatments to consider methods to assist with quitting.
5. Providers should use Motivational Interviewing (MI) techniques to assess a patient’s stage of change when discussing smoking cessation; Motivational Interviewing questions might also help a patient explore the costs and benefits of smoking cessation.
References

Altum, S. & Seltzer, J. (2013). Tobacco Cessation: How to Change?. Cincinnati Veterans Affairs Medical Center, Cincinnati, OH.


Panos, R. (2014). Lung Age Graph. (Unpublished.) Cincinnati Veterans Affairs Medical Center, Cincinnati, OH.
8 Fostering Patient Self-Management of COPD

Key Points
1. Healthcare providers play an important role in helping patients learn to actively self-manage their COPD.
2. The core skills needed to become a good self-manager include problem-solving, decision-making, resource utilization, formation of the patient-provider relationship, and taking action.
3. Self-management tasks that are important to patients with COPD include tobacco cessation, medication adherence, establishing an action plan for exacerbations, learning to cope with breathlessness, eating a healthy diet, and following an exercise plan.
4. Self-management programs offer interventions that not only educate but also empower patients and their families by supporting their efforts toward health improvement.
5. Decision-making should be shared between the clinician and the patient and will vary depending on the stage of disease and the individual focus of the patient (e.g., curative vs. healing).

8.1 Introduction

Chronic Obstructive Pulmonary Disease (COPD), like most other long-term health problems, requires more from medical providers than medication management alone. It necessitates a collaborative partnership between patient and provider. Patient understanding of and investment in efforts to manage symptoms can impact disease burden, quality of life, and healthcare utilization. Although the most challenging aspect of chronic disease management is the art of engaging patients in active self-management, many primary care and pulmonary providers receive little training in these skills and feel least prepared for this aspect of their practice.

8.2 Clinician Skills

Clinician skills that foster behavior change are quite important to the overall management of COPD, but are often ignored. Orleans (1988, cited in Prochaska, 1994, p. 62) reported that 66% of medical providers are pessimistic about their patients’ ability to change. This negativism can easily become the biggest obstacle to helping patients change. Patients and medical providers often feel hopeless about their circumstances and their ability to make improvements, which leads to a vicious cycle of poor health
outcomes. Clinicians need a basic understanding of the stages of change, as well as training in strategies such as motivational interviewing, to engage patients in efforts to improve their health. Interventions that are matched to the patients’ readiness for change and help the patients explore their reasons, needs, and ability to change are much more likely to be effective.

In a comprehensive review of COPD self-management, Effing et al. (2012) offer practical tips for stimulating behavior change. Durdock (2010) also provides tips for affecting behavior change in patients with chronic diseases. The following list incorporates their recommendations, which are also summarized in Table 8.1:

1. **Knowledge does not equal motivation.** Knowledge can be a useful tool in helping patients identify a need to change. However, the process of changing behavior happens over time and involves several other key ingredients. Patients need to consider their ability to make a change, how it will impact the lives of others, how they will cope with any losses associated with the change, and where and how the new behavior might fit into their daily lives.

2. **Non-adherence to a treatment plan does not mean the patient does not care.** There may be a number of barriers to accomplishing behavioral goals. Teaching patients to brainstorm alternative strategies and resources is an important skill-building task to address barriers. The skilled clinician will ask open-ended questions to help explore and resolve ambivalence about making a change. Fight the urge to think negatively about a patient who does not seem to put effort towards behavior change. It may be that the patient feels helpless or depressed. The clinician’s attitude can have a profound impact in either reinforcing the patient’s negatively skewed view or providing hope and compassion.

3. **It is the patient’s agenda.** The first question to ask might be, is this the patient’s goal that he or she created? The patient must be the one to set priorities and iden-
tify what is most important for him/her to change. The clinician may feel that quitting smoking is a priority but the patient may select to invest in pulmonary rehabilitation instead. Often success with a smaller, more feasible goal will eventually lead to approaching larger, more challenging goals in the future. Alternatively, the patient may feel overwhelmed and depressed by the debility of the disease and select to invest in psychotherapy first before any other behavior change is feasible. It is important to offer options to patients and to honor their choices.

4. **Spend more time focusing on the positive effects of adaptive behaviors than on the negative effects of poor health choices.** It is tempting to share information about all the dangers of smoking or inactivity. If this is a strong urge, ask the patient what they know about the negative effects first. For many patients, a lack of knowledge is not the problem (see Tip #1). It is more important for the patient to verbalize how life will be better if he/she is able to make the behavior change. The more the patient states his/her reasons, abilities, desires and needs to change, the greater the likelihood that change will occur (Miller, 2013).

5. **Stimulate patient responsibility by asking open-ended questions instead of giving advice or solving the problem for the patient.** Patients are more engaged and activated when asked, “What concerns you the most about COPD and your health in the next five years?” or “What might you do differently to prevent another hospitalization?” It may actually take less clinician time and energy to ask these open-ended questions than to think of two or three ideas for the patient to try, only to hear the response, “No, that’s not feasible for me.”

6. **Help patients formulate action plans that are action-oriented, time-limited and measurable.** Patients just starting to make self-management goals should focus on weekly action plans and would benefit from weekly support. As patients successfully complete weekly action plans, they may be ready to create monthly or quarterly plans. Self-management classes like the Chronic Disease Self-Management Program, Living Well with COPD, Tobacco Treatment classes, and weight management classes are ideal for building this skill and generating success.

7. **Highlight patient self-efficacy by asking them how confident they are on a scale from 1 to 10 (with 10 being the most confident) that they can accomplish their action plan.** Ask what makes it the number given and not a LOWER number. This leads the patient to again vocalize the reasons, abilities, desires, and needs for completing the plan. This repetition may seem like a waste of precious time. However, stating the reasons for change is the most critical factor associated with behavior change (Miller, 2013).

### 8.3 Stages of Change

A patient’s readiness for change is a crucial factor in all health behavior changes. Prochaska and DiClemente (1983) outlined the stages of change in their investiga-
tions of self-changers. They delineated five distinct stages in the Transtheoretical Model of Change (also known as the Stages of Change Model) that all self-changers progress through as they attempt to make a behavioral change. Generally, a person moves from being uninterested, unaware or unwilling to make a change (precontemplation), to considering making a change (contemplation), to deciding and preparing to make a change (preparation), to taking steps and problem-solving challenges or barriers (action), and to incorporating the change into a daily routine (maintenance). Relapses are usually inevitable and become part of the process of working toward permanent change. No matter what behavior is targeted for change, each stage is progressed through. No stage is skipped, although progress is often non-linear. Ambivalence about changes leads people to “recycle” through some stages several times. The Stages of Change model is discussed in more detail in Chapter 7.

8.4 Patient Self-Management Skills

Engaging patients in active self-management starts with Primary Care and often requires more intensive support and guidance from a variety of services to address a number of tasks. Self-management is generally understood as “the day-to-day tasks an individual must undertake to control or reduce the impact of disease on physical health status” (Clark, 1991, p. 5). Healthcare providers work with their patients to help them develop and sustain self-management. Self-management involves coping with direct physical symptoms and reduced ability as well as the psychosocial problems that may accompany COPD. Clark and colleagues (Clark, 1991) defined three tasks of good self-managers:

1. Have knowledge about the disease and treatment options in order to make informed decisions;
2. Complete tasks aimed at managing the condition;
3. Apply skills to manage psychosocial distress associated with the chronic illness.

The Social Cognitive Theory of self-management emphasizes the development of core skills needed to become a good self-manager (Lorig, 2003). These skills include: problem solving, decision-making, resource utilization, formation of the patient-provider relationship, and taking action. Workbooks and exercises lead patients to build these skills, often in individual case management visits or in patient education classes. Skill mastery is accomplished through completion of short-term action plans. This new competence leads to increased confidence and self-efficacy, which is the belief that one can successfully complete the desired task/behavior (Bandura, 1977). Improved self-efficacy is predictive of lasting behavior change.
Fostering Patient Self-Management of COPD

8.5 Self-Management Tasks

COPD-specific self-management tasks are a significant part of successful treatment. Zwerink and colleagues (Zwerink, 2014) completed a comprehensive review of COPD self-management studies and identified six tasks that are common to the various self-management curricula: 1) medication adherence, 2) exacerbation action plans, 3) smoking cessation, 4) coping with breathlessness, 5) healthy diet, and 6) exercise plan. A workgroup of COPD self-management experts concurred that all of these tasks except for medication adherence are essential to successful self-management of COPD (Effing, 2012). Table 8.2 depicts the prevalence of each task in the studies reviewed.

Medication adherence, exacerbation action plans, coping with breathlessness, healthy diet, and exercise plans specific to COPD will be discussed in depth in this chapter. Smoking cessation – perhaps the most important self-management task for patients with COPD – is discussed in detail in Chapter 7. Coping with psychosocial distress related to chronic illness is also an important self-management task that will be discussed further in Chapter 13. Energy conservation strategies (e.g., pacing of activities) will be reviewed briefly in this chapter and will be covered in more detail in Chapter 14.

Benzo et al. (2013) recommend offering patients a choice of a variety of self-management options. Graphic representations and worksheets may facilitate the selection process and serve to:

1. Educate the patient about all of the tasks involved in successful COPD self-management;
2. Allow the patient to explore and understand each option to make an informed decision;
3. Provide a worksheet to spell out a specific action plan to initiate change; and
4. Act as a reminder of all of the tasks and the behavioral plan.

Table 8.2: Prevalence of Tasks in COPD Self-Management Curricula

<table>
<thead>
<tr>
<th>Self-Management Task</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication Adherence</td>
<td>87%</td>
</tr>
<tr>
<td>Action Plan for Exacerbations</td>
<td>74%</td>
</tr>
<tr>
<td>Tobacco Cessation</td>
<td>74%</td>
</tr>
<tr>
<td>Coping with Breathlessness</td>
<td>57%</td>
</tr>
<tr>
<td>Healthy Diet</td>
<td>57%</td>
</tr>
<tr>
<td>Exercise Plan</td>
<td>48%</td>
</tr>
</tbody>
</table>

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3. Provide a worksheet to spell out a specific action plan to initiate change; and
4. Act as a reminder of all of the tasks and the behavioral plan.
Two examples of these agenda-setting tools are *My COPD Choices* (Figure 8.1) and *COPD Self-Management Choices* (Figure 8.2).

### 8.5.1 Medication Adherence

One specific behavior that is unique to COPD and requires special attention is proper inhaler use (see Chapter 15, *Correct Inhaler Techniques*). Patients are often confused about:

1. Which inhalers to take at what time;
2. The difference between short-acting and long-acting inhalers;
3. Whether a spacer is necessary;
4. How to properly use inhalers to get the most benefit.

Patients’ poor compliance with COPD medications has been documented for decades (Windsor, 1980; Kaplan, 1990; Dolce, 1991; George, 2005; Krigsman, 2007a, b). Across studies, an average of 60% of COPD patients do not adhere to inhaler therapy over time (Chryssidis, 1981; Taylor, 1984; Dompeling, 1992; Bosley, 1994; Krigsman, 2007a,
b; Haupt, 2008) and up to 85% do not use their inhalers correctly (Crompton, 1990; Thompson, 1994; Van Beerendonk, 1998; van der Palen, 1995, 1998; Hesselink, 2001; Serra-Batlles, 2002). The most common self-reported reasons for poor adherence to inhaler use are forgetting (51%) and consciously deciding not to use it when feeling good (31%; Dolce, 1991).

In a review by Restrepo et al. (2008), regular instruction, supervision, and re-demonstration of proper inhaler technique were recommended to improve inhaler adherence. It is well recognized that demonstration and supervised practice with inhalers are far superior to written instruction alone. Another visual aid that can reduce confusion and improve compliance is the Cincinnati VAMC Respiratory Medications Visual Pillbox (Figure 8.3), which displays pictures of all inhalers on the formulary classified by type of inhaler and spacer use if applicable, and denotes dosing schedules. Inhalers prescribed for a particular patient are circled and the dosing times are checked by the provider. The Visual Pillbox is used in conjunction with inhaler demonstrations and practice. To assist with re-teaching, patients waiting to see their provider may be invited to watch videos demonstrating proper inhaler use. Providers can follow up by asking the patient about any differences between their technique and that portrayed in the video. (Correct inhaler use techniques are reviewed in Chapter 15, Practical Guide to Inhaler Use.)

Figure 8.2: COPD Self-Management Choices. This handout assists the patient with COPD in the selection of healthy behaviors related to COPD and is another example of an agenda setting tool that might aid patients in their management of their COPD.
Figure 8.3: Visual Pillbox. The Cincinnati VAMC Respiratory Medications Visual Pillbox is a visual medication aid that can reduce confusion and improve medication adherence. Pictures of all inhalers on the formulary are classified by type of inhaler and spacer use (if applicable) and the dosing schedule is pictorially displayed. Inhalers prescribed for a particular patient are circled and the dosing times are checked by the provider. The Visual Pillbox should be used in conjunction with inhaler demonstrations and practice.
Although improving patient comprehension may be helpful for some, other barriers to compliance should be considered as well. Patients with poor medication compliance are less likely to have a strong sense of faith and trust in their provider, they are more likely to rely on natural remedies, and they have low confidence in treatment effectiveness (George, 2005). To a lesser extent, non-adherence is associated with the complexity of the medical regimen, patient concerns about side-effects, the cost of treatment, and the number of medications the patient is prescribed. Underuse, especially in periods of increased symptoms and respiratory distress, is a common problem that might also be related to depression. Depressed patients are three times more likely to be noncompliant with treatment regimens (DiMatteo et al., 2007).

8.5.2 Exacerbation Action Plans

Reduced frequency of hospitalizations has been a major focus in COPD self-management studies. The financial burden of hospitalization is considerable given that 34% of patients are readmitted for respiratory issues within 90 days of discharge (Bucknall, 2012). Initial hospitalization and readmittance may occur because patients have trouble identifying exacerbation symptoms. The subsequent delay in seeking treatment (Rice, 2010; Bourbeau, 2003) increases the need for more intensive treatment, such as hospitalization. Researchers have concluded that exacerbation action plans can help patients become better able to identify symptoms and implement appropriate treatment plans, thereby reducing delays in intervention, preventing or reducing hospital stays, and promoting quicker recovery. Exacerbation action plans have also demonstrated effectiveness for asthma, congestive heart failure, and diabetes (Ofman, 2004).

There is evidence that COPD exacerbation action plans improve health-related quality of life (Zwerink, 2014). A meta-analysis of nine studies indicated that when self-management interventions included an exacerbation action plan, the risk of a respiratory hospital admission was reduced (Zwerink, 2014). Bischoff et al. (2011) concluded that exacerbation action plans were associated with a decrease in the number of days to recovery and associated with reduced healthcare utilization. However, exacerbation action plans did not necessarily reduce hospitalizations (Bischoff, 2011; Trappenburg, 2011), particularly when there was limited follow-up or education about the plans (Walters, 2010). While many studies have shown COPD exacerbation plans to be effective, not all have consistently yielded positive results. In fact, one study was terminated before completion because of a higher rate of death in the intervention group (Fan, 2012). The researchers hypothesized that a theory-based comprehensive care management program, an individualized treatment action plan for worsening COPD symptoms, and telephone case management would reduce the risk of COPD-related hospitalizations for patients who have severe COPD and are at risk for hospital admission. The study was stopped after an imbalance in mortality between the usual
care group and intervention group was discovered. When the study was terminated, 28 patients in the intervention group had died, compared to 10 patients in the usual care group. Despite extensive data analysis, no individual factors or combination of factors plausibly explained the differences in mortality (Fan, 2012).

There are emerging data that outline more specific characteristics of patients who benefit from exacerbation action plans. Gadoury and colleagues (2005) found several patient characteristics that predicted reduced hospitalizations, including being female, having a higher level of education, and increased walking capacity. Bucknall et al. (2012) identified patient activation or readiness for change, younger age, and living with other people as critical factors for patients to be successful self-managers and have fewer hospitalizations.

In sum, the research to date remains fairly inconclusive about the clinical effectiveness of exacerbation action plans. The proposed Department of Veterans Affairs/Department of Defense [VA/DoD] Guidelines for COPD (2014) recommend the use of exacerbation action plans only within the context of close monitoring by providers to ensure supported self-management. As such, treatment effectiveness and successful mastery of the action plan must be assessed continuously to ensure comprehension and adherence. Symptom diaries, enlisting caregiver support, and self-report regarding adherence are possible strategies that will allow the provider to better support the patient’s treatment adherence.

### 8.5.3 Coping with Breathlessness

Dyspnea, or breathlessness, is a multi-factorial symptom that involves both pathophysiologic and psychosocial factors. A cardinal feature of end-stage COPD, dyspnea can lead to high levels of distress and anxiety. Patients can benefit from having a thorough understanding of the causes of dyspnea (e.g., air trapping) and various self-management strategies they can use to gain a greater sense of control over their breathing. The most effective non-pharmacological treatments for dyspnea include pursed-lip breathing and pulmonary rehabilitation, although other strategies, such as abdominal breathing, yoga, and relaxation techniques, should be discussed to allow patients to decide what works best for them (Allen, 2010; see Chapter 14, Management of Stable COPD). Although a systematic review conducted by Holland et al. (2012) did not find evidence for consistent effects of pursed-lip breathing, abdominal breathing, and yoga on dyspnea or health-related quality of life, participants did experience improvement in exercise capacity.

Among patients with COPD, higher levels of anxiety and depression are associated with increased fatigue, dyspnea, and frequency of respiratory symptoms (Doyle, 2013). Dyspnea may occur in earlier stages of COPD in some patients, usually among females with comorbid anxiety and depression (Di Marco, 2005). Psychotherapy has been found to be useful for the treatment of depression and adjustment to chronic
illness but is not directly effective in addressing dyspnea (Marciniuk, 2011). However, patients hospitalized with COPD exacerbations have demonstrated reductions in dyspnea, depression, and anxiety after learning controlled breathing techniques from a respiratory therapist (Valenza, 2014). Thus, learning to manage breathing independently can help to improve overall quality of life for patients with COPD. See Chapter 13, COPD’s Effects on Psychosocial Functioning and Familial Interactions, for more information about the relationship between depression, anxiety, and COPD.

8.5.4 Exercise

Patients with COPD might find exercise to be too physically difficult to incorporate into their daily routines or they might feel overwhelmed by the amount of time and energy they are already contributing to self-managing COPD. Additionally, dyspnea can limit physical functioning. However, exercise programs, breathing retraining, and breathing exercises have been shown to reduce dyspnea and improve quality of life (VA/DoD, 2014). The proposed VA/DoD Clinical Practice Guideline for the Management of Chronic Obstructive Pulmonary Disease (2014) suggest that supervised exercise programs be provided to patients who have limited physical capabilities due to dyspnea.

Casaburi et al. (1997) investigated the effect of exercise tolerance and physiological responses in patients who have COPD. The researchers found that patients with severe COPD who exercise rigorously and regularly improve exercise breathing patterns and lower ventilation, both of which are associated with improved exercise tolerance. McNamara et al. (2013) suggested aquatic exercise for individuals who feel more comfortable with low-impact exercise. They concluded that aquatic exercise provides as much physical benefit (e.g., improve walking distance) as land-based exercise, and actually improves endurance exercise more than land-based exercise. Leung et al. (2013) determined that Sun-style t’ai chi is an effective moderate exercise for people with COPD, and can result in a number of health benefits (e.g., increased endurance shuttle walk time). For patients who are unable to participate in physical exercise because of dyspnea, the VA/DoD guidelines (2014) recommend offering breathing exercises to patients. One such breathing intervention is inspiratory muscle training (IMT). Inspiratory muscle training focuses on increasing the strength of the inspiratory muscles (e.g., the diaphragm) using a device or pursed lip breathing. Even when used as a stand-alone therapy, IMT is effective in strengthening inspiratory muscles, decreasing symptoms of dyspnea, and improving exercise capacity (Gosselink, 2011; Geddes, 2008). Finally, exercise has been shown to improve mental functioning. Emery et al. (2001) suggest that individuals with COPD have difficulty with fluid intelligence (the ability to take in new material and make sense of it). The researchers determined that just 20 minutes of exercise at peak levels (based on an individual’s heart and breathing rates) improves mental functioning.
8.5.5 Nutrition

Proper nutrition is particularly important for patients with COPD who require more energy than individuals with normal lung functioning to acquire and utilize oxygen (Allen, 2010). Being underweight increases the risk of mortality for patients with COPD (Schols, 1993). Even patients with stable COPD can experience weight loss due to the disease, which highlights the importance of identifying and addressing weight changes quickly and effectively. Nutritional screening should focus on assessing BMI and weight change, the latter of which is defined as weight loss of more than 10% of one’s body weight in the past six months, or more than 5% of one’s body weight in the past month (Celli, 2004). Weight loss (i.e., imbalance between energy expenditure and dietary intake) and muscle wasting (i.e., imbalance between protein synthesis and breakdown) contribute to the disability and mortality experienced by patients with COPD. As such, nutritional interventions may need to be combined with an exercise regimen in order to provide benefit to the patient (Creutzberg, 2003).

Patients should be educated about ways to obtain adequate caloric intake while choosing foods that do not raise carbon dioxide levels (i.e., choosing complex carbohydrates and healthy fats rather than simple carbohydrates and protein). Nutritional recommendations that might be made to all patients, such as watching salt intake, avoiding overeating, and staying hydrated, become particularly important for patients with COPD, whose ability to breathe and expel mucus are strongly impacted by these behaviors. Meal tips that may be beneficial for patients include sitting at the table while eating to encourage good posture and allow the diaphragm to work properly, taking small bites and chewing slowly to prevent overeating, resting before eating to maintain energy during the meal, and drinking fluids at the end of the meal to allow room for food (Allen, 2010).

8.6 Self-Management Programs

There are outstanding resources available to support patients with COPD and the healthcare teams who treat them. Self-management programs specific to COPD include pulmonary rehabilitation and Living Well with COPD (www.livingwellwithcopd.com, 2014). Other self-management programs, including the Chronic Disease Self-Management Program, tobacco treatment, and weight management programs, are also excellent options to empower patients and support their efforts toward health improvement. A few of the above-mentioned programs will be reviewed to address their unique contributions to COPD management.
8.6.1 Pulmonary Rehabilitation

Pulmonary rehabilitation (PR) primarily focuses on building physical strength and endurance through a supervised, graded exercise program that occurs several times per week. The American Thoracic Society (ATS) and the European Respiratory Society (ERS) recently updated their definition of pulmonary rehabilitation (Spruit, 2013, p. e14):

“Pulmonary rehabilitation is a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies that 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 to health-enhancing behaviors.”

Most PR programs are multi-disciplinary and include weekly education and support sessions to address a number of self-management tasks. Topics may include basic education about COPD and how to manage it, proper medication use, nutrition, energy conservation, coping with difficult emotions, and breathing strategies. There are a number of positive outcomes associated with pulmonary rehabilitation, including reduced dyspnea, increased exercise capacity, and improved quality of life (Spruit, 2013). Similar results were found in a systematic review of 18 randomized clinical trials that focused on home-based programs, which suggests that home-based pulmonary rehabilitation is an acceptable alternative to clinic-based programs (Liu, 2014). Recent research has also added the following new advances (Spruit et al., 2013, p. e14):

- There is increased evidence for use and efficacy of a variety of forms of exercise training as part of pulmonary rehabilitation; these include interval training, strength training, upper limb training, and transcutaneous neuromuscular electrical stimulation.
- Symptomatic individuals with COPD who have lesser degrees of airflow limitation and participate in pulmonary rehabilitation derive similar improvements in symptoms, exercise tolerance, and quality of life as do those with more severe disease.
- Pulmonary rehabilitation initiated shortly after a hospitalization for a COPD exacerbation is clinically effective, safe, and associated with a reduction in subsequent hospital admissions.
- Exercise rehabilitation commenced during acute or critical illness reduces the extent of functional decline and hastens recovery.
- Appropriately resourced home-based exercise training has proven effective in reducing dyspnea and increasing exercise performance in individuals with COPD.
- The scope of outcomes assessment has broadened, allowing for the evaluation of COPD-related knowledge and self-efficacy, lower and upper limb muscle function, balance, and physical activity.
- Symptoms of anxiety and depression are prevalent in individuals referred to pulmonary rehabilitation, may affect outcomes, and can be ameliorated by this intervention.
8.6.2 Living Well with COPD

Living Well with COPD is a self-management program that teaches patients with COPD the skills necessary to manage their illness in a collaborative environment designed to enhance self-efficacy and motivation for change. The goal of Living Well with COPD is to “develop a partnership between patients and healthcare professionals to facilitate the adoption of healthy lifestyle behaviors and the skills needed to better manage COPD on a day-to-day basis” (Nault, 2006). Drawing from the chronic care model (Wagner, 2001), the Chronic Disease Self-Management Program (Lorig, 2003), and the Precede-Proceed Model (Green, 1999), Living Well with COPD provides educational interventions that are tailored to the learning needs of individual patients and are designed to enhance self-efficacy, increase motivation to create and maintain behavioral change, and facilitate mastery of self-management skills. The objectives of the program are to help patients improve quality of life, maximize autonomy, prevent and manage progression of the disease, and help caregivers support the patients’ efforts to achieve behavioral change.

Living Well with COPD can be completed on a weekly basis in individual sessions, a group setting, or as part of a pulmonary rehabilitation program. The program consists of seven skill-oriented modules that provide detailed information related to self-management of various facets of COPD (e.g., medication compliance, controlling breathlessness, prevention and management of exacerbations). The patient education process requires that the educator utilize the following steps:
1. Assessment of readiness and motivation to learn,
2. Setting mutually realistic learning goals and objectives,
3. Use of efficient educational methods,
4. Implementation of educational objectives, and
5. Evaluation of patients’ learning outcomes (e.g., direct questioning, problem solving, repetition of key instructions).

Effective provision of the Living Well with COPD program requires that the provider (i.e., any health care professional willing to devote time to this process) have both expertise regarding proper management of COPD as well as empathy and enthusiasm for the patients and their journey toward effective COPD self-management through long-term behavior change. (Patients and providers can learn more about the program at www.livingwellwithcopd.com.)

Utilization of the Living Well with COPD program yields positive outcomes. In a one-year, multi-site, randomized clinical trial, the program improved quality of life, reduced hospitalizations and emergency department visits for COPD exacerbations by 40%, and decreased unscheduled medical visits by nearly 60% (Bourbeau, 2003). Another one-year, multi-site, randomized clinical trial conducted by Gadoury et al. (2005) found that participants of the Living Well with COPD program continued to demonstrate reductions in all-cause hospitalizations (27%) and all-cause emergency visits (21%) at the end of a two-year follow-up period.
8.6.3 Chronic Disease Self-Management Program

Disease-specific education is necessary but not sufficient to produce patient actions related to managing the disease (Becker, 1980). Becoming a better self-manager is linked to learning how to set goals, organize resources, and use problem-solving strategies (Clark, 1991). Bodenheimer et al. (2002) indicated that self-management classes that included action planning were more likely to improve health outcomes, particularly for participants with more severe symptoms.

The Chronic Disease Self-Management Program (CDSMP), which was created by Kate Lorig, Virginia Gonzalez, and Diana Laurent, focuses on developing self-management skills needed to manage effectively any chronic health condition by teaching goal-setting, problem-solving, and action planning (Lorig, 2012). This structured treatment, led by healthcare professionals and/or lay leaders, is unique in its ability to address a number of health problems in one group format. Patients with comorbid chronic conditions can benefit from the patient education approach, which focuses on improving breathing, healthy eating, physical activity, medication usage, dealing with difficult emotions, relaxation strategies, positive thinking, and communication skills. However, the true lasting benefit from the program is the skill building that takes place around brainstorming, problem solving, and action planning. Each class incorporates an opportunity to brainstorm, a process where ideas are quickly generated without being questioned or censored to allow for the most creative and extensive list possible. Participants also learn and practice a problem-solving method that encourages them to consider and try alternative strategies, which provides a greater sense of control and improves investment in care.

Action planning in CDSMP helps participants work toward goals of their choice during and between each class. Participants may choose any goal, as long as it meets the criteria listed in Table 8.3 (Lorig, 2001). Initially, participants may struggle to meet all these criteria, perhaps choosing things that will not fit into their schedule, are more strenuous than they can handle, or involve resources they may not have. The group is utilized to brainstorm ways to make the plan more specific or practical and build the participants’ confidence in their ability to succeed. The following session involves progress reports and brainstorming by the group to identify strategies that can make the goal more feasible. Through this process, participants learn to make action plans that they can accomplish. They build on small successes and become more confident in their ability to feel in control of their symptoms and their lives.

Lorig et al. (2001) conducted a two-year follow-up study that looked at health status, health care utilization and self-efficacy outcomes for 831 participants 40-years or older with heart disease, lung disease, stroke, or arthritis. Participants who completed at least four of six CDSM sessions had significantly fewer ER and outpatient visits, declines in self-reported health distress, and improvement in perceived self-efficacy. Bodenheimer et al. (2002) reported that patients attending self-management classes had fewer hospitalizations over a six-month period compared to con-
Shared decision-making is the clinical process that occurs when providers share treatment options, including risks and benefits, and patients weigh their options based on their values and beliefs. While shared decision-making might be most critical when considering end-of-life care, it should be a vital part of all stages of chronic disease management. Clinicians provide the expert information about treatment options, risks, and benefits. Patients feel empowered to use the information to make the choices that fit them best.

Shared decision-making is supported by a focus on whole person care (Hutchinson, 2011), which broadens the scope of clinical interactions to include all aspects of the patient’s life, including physical, emotional, and spiritual factors. A whole person assessment expands beyond a physical exam to include conversations about supportive relationships, meaningful activities, stable safe housing, physical activity, healthy eating, stress and sleep, and active involvement in medical care. This process offers the opportunity for patients and providers to gain a full picture of all aspects of life and how they interact. Creating this unique perspective of one’s life allows the patient to see strengths and areas in which progress is being made. Patients may also start
Chronic disease management calls upon the medical provider and the patient to choose between two areas of focus: curative or healing (Hutchinson, 2011) (Table 8.4). Patients who seek a cure are focused on survival and maintaining all things in life prior to disease onset, which leads to efforts to avoid change, whether adaptive or maladaptive. Patients seeking a cure often have an external locus of control and feel powerless to improve their situation. They look to medical professionals to “fix” the problem. Those seeking a cure are in the precontemplation stage of change and often use defense mechanisms such as externalizing, blame, and denial. Alternatively, patients who are able to shift to a healing perspective are accepting of change. They develop a new identity and are able to recognize that their own actions and efforts can

Figure 8.4: Wheel of Health. The *Cincinnati VAMC Personalized Health Plan Wheel of Health* is an example of a patient handout that can be used to facilitate a whole person assessment. The patient is asked to review each area of health and determine whether they are doing well, are working on improvements, or want to work on improvements. The Wheel of Health provides the patient with a self-assessment tool that can also be used by providers to explore those areas that the patient has identified as important and, potentially, those areas that they are interested in improving.
help them obtain functional improvement and satisfaction. The shift from a curative focus to a healing focus is commonly referred to as adjustment to chronic illness.

The role of the provider varies depending on whether the patient is in “curing” mode or “healing” mode. If the patient is focused on finding a cure, the provider can use scientific knowledge to assess symptoms and arrive at a diagnosis. The focus is on the use of algorithms, symptom constellations, physical exam, and test results. Evidence-based treatments are prescribed. When the patient is focused on “healing” – or palliative care – a collaborative patient-provider relationship is necessary. Rather than directing an assessment using an algorithm, the provider can offer treatment options but follow the patient’s wishes as the patient shares what he/she would like to change, how important the change is, and how he/she would like to make it. A team approach is often most effective and fosters an environment of support and guidance that is important for behavioral changes. This whole person approach relieves suffering and promotes healing, particularly in COPD care. The process helps foster a sense of wholeness and balance. Patients identify what really matters in their lives, and clinicians use this information to better align the patients’ health goals and behaviors with their priorities.

Of note, as disease severity increases, the treatment often shifts from being patient-driven to provider-driven. In the early stages of COPD, patients are physically able to invest in exercise programs and self-management classes, which reduces disease burden and improves functioning. Having a positive attitude about patients’ ability and desire to improve is critical during this phase. Adjustment to disease, readiness for change, anxiety, and depression are all possible complicating factors that may make behavior change more challenging. A perspective of whole person

<table>
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<tr>
<th>Curative</th>
<th>Healing / Palliative</th>
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<td>Patient:</td>
<td>Patient:</td>
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<tr>
<td>- Is focused on survival</td>
<td>- Accepts change</td>
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<tr>
<td>- Is focused on maintaining “pre-diagnosis” life</td>
<td>- Develops new identity</td>
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<td>- Avoids changes</td>
<td>- Recognizes power in situation</td>
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<td>- Feels powerless to improve situation</td>
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<td>- Looks to health care professionals to fix it</td>
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<td>- Externalizes, blames, denies</td>
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<td>Provider:</td>
<td>Provider:</td>
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<tr>
<td>- Uses scientific knowledge to assess symptoms and diagnosis</td>
<td>- Follows patient’s lead</td>
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<tr>
<td>- Focuses on symptom constellations, physical exam and test results</td>
<td>- Offers treatments based on patient’s preferences</td>
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<tr>
<td>- Prescribes treatments</td>
<td>- Works within a team</td>
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<tr>
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<td>- Uses a whole person approach</td>
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health, including physical, emotional, and spiritual health, can help to identify these potential barriers and lead patients to appropriate resources. As COPD progresses, physical limitations increase, and other comorbid conditions impact health, patients become more reliant on medical providers for direction and support. Again, anxiety and depression may develop as patients develop fears about dying and feel that their situation is hopeless.

8.8 End-of-Life Discussions

Advanced stages of COPD require a shift in care choices to address end-of-life issues. The primary care provider is often identified as the most appropriate person on the healthcare team to initiate this discussion. Timing of the discussion may be difficult to gauge. The American Thoracic Society recommends that it take place when the patient is stable rather than during an acute exacerbation or hospitalization (American Thoracic Society, 2014). Lanken et al. (2007) argue that palliative care discussions are appropriate anytime there is an exacerbation of symptoms. Discussions about restorative measures are likely to occur simultaneously with options for palliative care.

Curtis et al. (2004) reported that only about a third of patients with COPD discuss end-of-life choices with their primary care provider. As compared to patients with other life-threatening illnesses like cancer and HIV, COPD patients are less satisfied with the information they receive from their healthcare provider about COPD, its course, and end-of-life planning (Curtis, 2004). One complicating factor for providers is the large variability of decline. Patients with very severe impairment can live an average of three years (Celli, 2004), adding to the challenge of when to initiate the end-of-life discussion.

Au et al. (2011) found that COPD patients want to know how long they have to live and what dying might be like and they would like their providers to ask them about their religious beliefs and their feelings about disease progression. While this discussion is best initiated by the primary care provider, it is clearly a topic about which all members of the integrated care team should be well informed and prepared to address. The discussion is likely to happen over a series of visits with different members of the team. It is worthy of revisiting after acute episodes, whether hospitalization was necessary or not. Au et al. (2011) suggest that providers create a standard statement that might help initiate the end-of-life conversation (e.g., “This is something I talk about with all my patients to make sure I understand their wishes.”). Core skills of motivational interviewing, reflections, and open-ended questions are useful to explore and clarify the patient’s preferences, values, and wishes. Examples of standard statements and open-ended questions can be found in Table 8.5. (See Chapter 19, Palliative Care and Hospice, for more information about end-of-life issues.)
8.9 Integrated Care Teams

All self-management studies of COPD agree that a multifaceted approach from an integrated care team is most effective. Wagner (1998) supports an integrated team approach in his Chronic Care Model. His model focuses on Primary Care as the hub and the patient-provider relationship as critical to health improvement. Across studies, key ingredients of services tend to vary, making it difficult to discern whether an ideal combination exists. Patient preference and disease severity are two factors that might impact the options for integrated team members/services. Table 8.6 outlines possible available options and attempts to categorize the service based upon disease severity and the addressed needs and skills. These suggestions are based on the COPD Specialty Care Neighborhood Project at the Cincinnati VAMC (2011–2014).

8.10 Conclusion

Effective self-management of COPD requires active collaboration between the provider and the patient. This alliance will help facilitate patient understanding of and investment in effective disease management which can impact disease burden, quality of life, and healthcare utilization. Self-management strategies should focus on tobacco cessation, medication adherence, establishing an exacerbation action plan (with close monitoring) to intervene early and prevent full-blown exacerbations and hospitalizations, using effective breathing techniques, eating a healthy diet, and following an exercise plan. Patients can benefit from a variety of self-management programs (e.g., pulmonary rehabilitation, Living Well with COPD, Chronic Disease Self-Management Program) that are designed to provide education about COPD, increase motivation to create and maintain behavioral changes, and teach skills necessary to problem-solve when barriers to effective symptom management arise. Providers should utilize strategies to stimulate and support behavior change in patients by maintaining awareness of how a patient’s stage of change and approach to managing chronic illness (i.e., curative or healing) are individually and collectively impacting the patient’s self-management behaviors. By taking a whole person approach to treatment, providers can help patients feel empowered by their strengths and recognize the areas in which
## Table 8.6: Effect of COPD Severity on Skills Offered by Integrated Team Members/Services

<table>
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<tr>
<th>Disease Severity</th>
<th>Type of Service</th>
<th>Skill Building Offered</th>
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<tbody>
<tr>
<td>1–4</td>
<td>Primary Care Provider</td>
<td>1. Diagnoses&lt;br&gt;2. Medication management&lt;br&gt;3. Referral for self-management</td>
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<tr>
<td>1–3</td>
<td>RN Care Manager in Primary Care</td>
<td>1. Inhaler teaching&lt;br&gt;2. Individualized self-management training for COPD&lt;br&gt;3. Transitions of care – Inpatient, Primary Care, Pulmonology&lt;br&gt;4. Referral to self-management&lt;br&gt;5. Monitoring of exacerbation action plan</td>
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<tr>
<td>1–3</td>
<td>Clinical Pharmacist</td>
<td>1. Initial inhaler teaching&lt;br&gt;2. Individualized self-management training for COPD</td>
</tr>
<tr>
<td>1–2</td>
<td>Other Related Self-Management Programs Tobacco Treatment Weight Management Classes</td>
<td>1. Action planning&lt;br&gt;2. Building self-efficacy</td>
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<tr>
<td>2–3</td>
<td>COPD Case Manager in Pulmonary Clinic</td>
<td>1. Inhaler teaching&lt;br&gt;2. Individualized self-management training for COPD&lt;br&gt;3. Symptom management&lt;br&gt;4. Transitions of care – Inpatient, Primary Care, Pulmonology&lt;br&gt;5. Monitoring of exacerbation action plan</td>
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| 1–4              | Primary Care Provider               | 1. Diagnoses  
2. Medication management  
3. Referral for self-management |
| 1–3              | RN Care Manager in Primary Care     | 1. Inhaler teaching  
2. Individualized self-management training for COPD  
3. Transitions of care – Inpatient, Primary Care, Pulmonology  
4. Referral to self-management  
5. Monitoring of exacerbation action plan |
| 1–3              | Clinical Pharmacist                 | 1. Initial inhaler teaching  
2. Individualized self-management training for COPD |
| 1–2              | Chronic Disease Self-Management Classes Ex., Living Well with COPD, Chronic Disease Self-Management Program | 1. Problem-solving  
2. Action planning  
3. Decision-making  
4. Partnering with providers  
5. Building self-efficacy |
| 1–2              | Other Related Self-Management Programs Tobacco Treatment Weight Management Classes | 1. Action planning  
2. Building self-efficacy |
| 1–2              | Telephone Support, Text Support, Secure Email and Mobile Apps for Self-Managementa | 1. Action planning  
2. Problem-solving  
3. Building self-efficacy  
4. Maintaining improvements long-term |
| 1–2              | Shared Medical Appointment for COPDb | 1. Medication management  
2. Inhaler teaching  
3. Symptom management  
4. Action planning |
| 2–3              | COPD Case Manager in Pulmonary Clinic | 1. Inhaler teaching  
2. Individualized self-management training for COPD  
3. Symptom management  
4. Transitions of care – Inpatient, Primary Care, Pulmonology  
5. Monitoring of exacerbation action plan |
| 2–3              | Home Telehealth Nurse for COPDb | 1. Adherence to medication  
2. Problem-solving  
3. Decision-making  
4. Action planning  
5. Symptom management |
they can take more responsibility for their own well-being. Providers can also engage patients in discussions about end-of-life care to ensure that patients have the opportunity to receive answers to their questions and to express their wishes.

### 8.11 Summary Points

1. Learning specific skills (e.g., problem-solving, resource utilization, taking action) can help patients feel more confident in their ability to initiate and maintain long-term behavioral change.

2. While tobacco cessation is perhaps the most important self-management task, patients who effectively manage COPD also succeed in implementing other self-management strategies (e.g., medication adherence, using an action plan for...
exacerbations, learning to cope with breathlessness, eating a healthy diet, and following an exercise plan).

3. Behavior change is a complex process that occurs over time. Self-management programs, such as pulmonary rehabilitation, Living Well with COPD, and the Chronic Disease Self-Management Program offer more intensive support, skill building, and translation of skills to everyday life.

4. Clinicians should have a basic understanding of the stages of change in order to match interventions to the patients’ readiness for change which is clarified through exploration of the patient’s motivations, needs, and abilities.

5. Collaborative end-of-life discussions involving the patient and family members should be conducted in a way that respects the patient’s current stage of acceptance but also calls attention to the importance of making end-of-life decisions as early as possible.

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9 Natural History, Phenotypes, and Gender Differences in COPD

Key Points

1. COPD is a heterogeneous group of diseases characterized by persistent airflow obstruction with a variable rate of decline in lung function.
2. Progression of lung function decline varies and is dependent upon continued smoking, presence of emphysema, responsiveness to bronchodilators, and acute exacerbations of COPD.
3. The single best predictor for a COPD exacerbation is a history of prior exacerbations. Other risk factors include advanced disease, gastro-esophageal reflux, poorer quality of life, and elevated white blood cell count.
4. Different phenotypes of COPD vary in their clinical presentation, exacerbation rates, disease progression, and response to treatment. Current known phenotypes include asthma-COPD overlap syndrome, frequent exacerbation, emphysema predominant, mucus producers, and alpha 1-antitrypsin deficiency.
5. Gender differences in COPD include differential disease presentation, response to therapies, and health care delivery and utilization.

9.1 Natural History of COPD

Chronic Obstructive Pulmonary Disease (COPD) is a constellation of heterogeneous lung diseases characterized by persistent expiratory airflow limitation that is non-normalizing (does not return to predicted levels), and an abnormal inflammatory response of the lungs to noxious particles and gases such as cigarette smoking (GOLD, 2014). COPD is a preventable and treatable chronic lung disease with a wide range of systemic manifestations (reviewed in Chapter 10). Contrary to the classic belief (Fletcher, 1976), all patients with COPD do not experience progressive, accelerated decline in lung function; instead, the clinical presentation and disease course can be vastly variable among individuals and are influenced by numerous factors (Vestbo, 2011).

COPD is caused by several different and overlapping etiologies. Tobacco smoking is the leading cause of COPD worldwide. Smoking exposure in the form of cigarettes, cigars, water-pipes, or second-hand exposure also increases the risk of disease (Koeverden, 2014; Raad, 2011; Thun, 2013). Occupational and environmental exposures account for 20–30% of COPD cases. In urban areas, environmental air pollution (Tashkin, 1984) and working in dusty places (Melbostad, 1997) play roles in the development of COPD; whereas, in rural areas and developing countries, smoke generated from biomass fuels (Lopez, 2006) is a major risk factor. The risk of occupational and environmental exposures increases geometrically with concomitant tobacco smoke
exposure (Blanc, 2009). Significant inter-individual variation to the injury caused by these noxious particles is caused by different genetic susceptibilities that lead to modulation of the inflammatory response. A genome wide search (COPDGene) has identified multiple genes that are associated with COPD development and inter-person variations in disease manifestations (Castaldi, 2014; Cho, 2014).

Our ability to recognize the heterogeneity in pathophysiology and clinical course of COPD has led to the recognition of ‘phenotypes’ of COPD. The characterization of different phenotypes is essential as they can vary in clinical course, symptoms, response to different treatments, and prognosis (Mannino, 2013). One example of such a phenotype is the “frequent exacerbator” type. These patients experience multiple episodes of acute decompensation in respiratory status related to COPD called acute exacerbations of COPD. The disease course, health care utilization, and therapeutic options for this category of patients are different than for non-frequent exacerbators (Hurst, 2010). The treatment guidelines from the Global Initiative for Obstructive Lung Disease (GOLD, 2014) encourage physicians to identify this phenotype and adjust maintenance therapies accordingly.

It is also important to recognize that COPD is a systemic inflammatory disease with extensive and variable extra-pulmonary involvement (Agusti, 2013). Our understanding of these extra-pulmonary manifestations is evolving and their role in influencing the long term disease course and outcomes is unclear. Most longitudinal studies have used lung function (such as forced expiratory volume in 1 second, FEV1) as a hallmark of disease state. However, FEV1 may not be influenced by the numerous extra-pulmonary manifestations and, hence, may not correctly estimate the disease state or progression. This prognostic limitation of physiologic variables has led to the development of newer multi-dimensional approaches to assess disease severity and progression. One example of a multivariable assessment tool is the BODE index which is comprised of Body mass index, airflow Obstruction, Dyspnea, and Exercise capacity (Celli, 2004). Higher scores on the BODE index correspond to a higher risk of death. Searches for other surrogate markers to monitor disease progression and response to treatments are currently underway (Vestbo, 2008).

9.2 Factors Influencing Lung Function in COPD

A natural decline in lung function is observed as part of aging in healthy individuals. After reaching maximal lung growth, a plateau phase of lung function exists between 20 and 30 years of age (Figure 9.1). After this plateau phase, a healthy person may lose 1L of FEV1 in 50 years of adult life at an average rate of decline of 20 ml/year.

The natural history of lung function decline in COPD is influenced by multiple factors occurring over a person’s life span. The factors include early life events such as intra-uterine and childhood lung development, childhood-adolescent lung growth, and later life exposures such as smoking, occupational chemical, dust, and fume
In addition, genetic factors are also critically important. Each person may vary in lung function capacity at any given time in life and will experience different trajectories of lung function decline, as shown in Figure 9.1. The roles of factors that influence the lung function in COPD are described here and summarized in Figure 9.2.

### 9.2.1 Lung Growth and Early Life Events

In humans, the conducting airways are developed during intra-uterine life by 16 weeks of gestation (Ten Have-Opbroek, 1981). However, the development of gas exchange units (respiratory bronchioles and alveoli) continues throughout childhood into the early adolescent years. After eight years of life, the alveolar number does not increase any further and lung growth is then achieved by increases in the size of the alveoli and airways. Any significant life event during this period of lung development can reduce the maximum lung function that a person achieves in adulthood (Stern, 2007). Infant onset atopy, maternal asthma, and maternal smoking are associated with low

![Figure 9.1: The course of lung function (FEV₁) throughout life. Black line: lung function trend in healthy individuals. Purple lines: impaired lung growth due to various factors that influence “maximal lung growth”. Red lines: trends in lung function decline in patients with COPD. Trends in FEV₁ decline have variations based on different factors and phenotypes. The decline may not be a continuous trend as shown in the figure, but can also be a step-wise decline due to acute exacerbations of COPD. Green lines: effect of smoking cessation on lung function. The beneficial effect of smoking cessation may be variable at different stages of COPD as shown by different trajectories.](image-url)
Factors Influencing Lung Function in COPD

1. Maternal smoking \textit{in-utero}
2. Smoking exposure in childhood
3. Smoking exposure in adolescence
4. Childhood atopy
5. Maternal asthma

Factors reducing plateau phase

1. Smoking exposure

Factors accelerating lung function decline

1. Active smoking
2. COPD exacerbations
3. Presence of emphysema
4. Bronchoreactivity
5. Genetic susceptibility
6. Biomarker CC-16

Figure 9.2: Factors associated with reduced lung function in different phases of lung life. Lung function in patients with COPD is affected by multiple factors during the lung growth phase, plateau phase and declining lung function phase. Smoking exposure is a major contributor of reduced lung function in all phases of lung life. CC-16: Clara cell secretory protein 16

lung function that is detectable at 1 month of age and persists through 18 years of age (Turner, 2014). Cigarette smoking in adolescence also slows lung growth and reduces the maximally attained lung function (Gold, 1996). Therefore, the maximal lung function achieved by individuals can vary and these differences in “baseline” lung function may affect the onset of COPD in later life.

9.2.2 Cigarette Smoking

Smoking is the most influential factor affecting the natural history of COPD. It plays a role in disease development, severity of lung function impairment, frequency of exacerbations, and progression of disease. Maximal lung growth is reduced by maternal smoke exposure and smoking during the adolescent years while the lungs are still growing (Gold, 1996; Turner, 2014). During the ‘plateau phase’ of maximal lung function, smokers experience a premature onset of lung function decline which reduces the duration of this phase. In severe cases, the plateau phase may even become nonexistent (Tager, 1988). Finally, continued smoking most strongly affects the annual rate of lung function decline in patients with COPD. The rate of decline as measured by FEV$_1$ is 21 ml more per year in active smokers than non-smokers or previous smokers. Thus, an average active smoker will lose almost 40 ml/year of lung function compared with a natural 20 ml/year decline in healthy aging adults. The cumulative prior smoke exposure does not influence the annual rate of lung function decline (Vestbo, 2011).

Smoking cessation at any time during adulthood is expected to slow the rate of decline in lung function (Anthonisen, 2002). The magnitude of smoking cessation’s effect, however, may be variable at different stages of COPD, with a lesser change noted in advanced stages (Jha, 2013; Kohansal, 2009; Vestbo, 2011).
9.2.3 Genetic Susceptibility

COPD presents with heterogeneous clinical features and the smoking related injury to the lungs may vary among individuals (Burrows, 1964; Burrows, 1966). Genetic susceptibilities contribute significantly to the manifestation of these variations (Ingebrigtsen, 2010). Previously, the only proven genetic abnormalities that caused a predisposition to the development of COPD were mutations in the alpha 1-antitrypsin inhibitor gene – a serine proteinase inhibitor (Eriksson, 1964; Laurell, 2013). Concurrent tobacco smoke exposure further accelerates the lung function decline in patients with alpha 1-protease inhibitor mutations (Silverman, 1998). Recent large population based genome wide sequencing studies (COPDGene) have revealed strong genetic associations with development, severity, and phenotypes of COPD (Cho, 2012). Several gene loci such as CHRNA3, FAM13A, HHIP, RIN3, MMP12 and TGFβ2, have been associated with the development of moderate and severe COPD (Cho, 2014). Genetic associations have been linked to the pattern of distribution of emphysema in smokers. Mild upper zone emphysema is associated with rs1980057 near HHIP, and severe emphysema with rs8034191 on chromosome 15q region (Castaldi, 2014).

9.2.4 Advancing Age

COPD is associated with advancing age; however, it remains unclear if age itself is a risk for COPD or whether it reflects lung injury related to the cumulative effect of exposures throughout life. Human lung parenchyma loses elasticity with age which results in the development of airflow obstruction. In normal aging, this process is slow and does not lead to clinically significant respiratory impairment (Figure 1). In COPD, however, there is loss of lung parenchymal elasticity leading to air flow limitation and respiratory symptoms. Thus, COPD can be regarded as premature and accelerated aging of the lungs.

9.2.5 Emphysema

Emphysema is characterized by destruction of gas-exchanging air spaces. In genetically susceptible individuals, the response to lung injury from smoking or other noxious stimuli may lead to emphysematous changes (Castaldi, 2014). The presence and extent of emphysema can be assessed radiographically using computed tomography (CT) scans (Gietema, 2011). Emphysema is an independent risk factor for rapid decline in lung function. In the ‘Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints – ECLIPSE’ cohort, patients with emphysema had an additional 13 ml decline in their FEV1 annually compared to those without emphysema (Vestbo, 2011). Similar findings have been seen in other cohorts where emphysema is
associated with rapid decline (Nishimura, 2012; Yuan, 2009). The presence of emphysema also independently increases the risk of COPD exacerbations irrespective of the disease severity measured by FEV₁. Patients with emphysema that involves more than 35% of the lung parenchyma are at a higher risk for COPD exacerbations. The risk continues to increase by 1.18 fold for every 5% increase in emphysema area (Han, 2011). The rate of increase in the extent of emphysema is variable among individuals and is related to smoking and gender. A more rapid increase is observed in women and in active smokers (Coxson, 2013).

9.2.6 Bronchodilator Responsiveness

A subset of patients with COPD has a significant bronchodilator response measured by pulmonary function testing. These individuals experience a more rapid rate of decline in FEV₁ and lose an additional 17 ml yearly (Vestbo, 2011). They are at higher risk for exacerbations, hospitalizations, and worse health related quality of life (Hardin, 2011; Menezes, 2014). However, despite these distinct features, the presence and magnitude of bronchodilator responsiveness is not uniformly consistent and changes over time in this subset of COPD patients (Albert, 2012).

9.2.7 Early Disease

Diagnosing early stage COPD is essential but remains challenging for multiple reasons (Csikesz, 2014). First, patients do not experience disabling symptoms until the disease has advanced due to high baseline pulmonary reserves. Patients may also adapt their life style by reducing activity to compensate for their symptoms. Secondly, in the past, it was incorrectly thought that early diagnosis of COPD is a fruitless chore as the treatment does not alter the course of disease (Celli, 1995). Patients with early disease actually have a faster rate of lung function decline and an increased mortality primarily related to acute cardiac events (Sin, 2005; Vestbo, 2011). In the ECLIPSE cohort, patients with GOLD stage 2 disease (FEV₁ 80–50% of predicted) had a mean rate of FEV₁ decline of 35 ml/year, which was significantly higher than 33 ml/year for GOLD stage 3 and 25 ml/year for GOLD stage 4 patients (Vestbo, 2011). This inverse relationship between GOLD stage of airflow severity and rate of FEV₁ decline has been consistently noted in other long term studies (Calverley, 2007; Tashkin, 2008). Some patients with early disease have also shown evidence of lung function recovering with appropriate treatment (Galban, 2012; Vestbo, 2011). These findings have sparked interest to identify early COPD to prevent rapid decline, reduce mortality, and institute treatment with goals of complete normalization of lung function.
9.2.8 Biomarkers

Numerous biomarkers have been investigated to predict the disease course and identify various phenotypes. Among the few that have shown potential, serum fibrinogen level is most significantly associated with disease severity and exacerbation rate. Elevated serum white blood cell count level is also associated with increased exacerbations. Weak associations are observed with Clara cell secretory protein 16 (CC-16) and the rate of lung function decline (Faner, 2014; Hurst, 2010a; Vestbo, 2011).

9.3 Role of COPD Exacerbations and Progression of Disease

The disease course of COPD is punctuated with episodes of acute exacerbations which are associated with significant increases in health care utilizations, cost, and mortality (Miravitlles, 2002; Soler-Cataluna, 2005). Exacerbations are episodes of worsening of respiratory symptoms outside of normal day-to-day variations. They are associated with airway and systemic inflammation and increased dynamic hyperinflation (O’Donnell, 2006).

In the last two decades, the importance of exacerbations in lung function decline and worse patient outcomes has been increasingly recognized. Previously, based upon the work of Fletcher and Petro, exacerbations were thought to have an insignificant role in overall disease course (Fletcher, 1976). Acute exacerbations of COPD are now known to have both short and long term effects on disease course and outcomes. Given their deleterious impact on patients, reducing the rates and severity of COPD exacerbations has now become a widely accepted surrogate marker of treatment success in clinical trials. The following effects of exacerbations are observed in patients with COPD:

9.3.1 Lung Function Decline

Exacerbations accelerate the rate of lung function decline. Patients with frequent exacerbations have an almost 25% faster rate of FEV$_1$ decline compared to those who do not have frequent exacerbations (Donaldson, 2002; Kanner, 2001). Larger observational and interventional studies such as the UPLIFT trial and ECLIPSE cohort have confirmed that patients with frequent exacerbations have lower FEV$_1$ at any stage of the disease compared to those who do not have frequent exacerbations (Halpin, 2012; Vestbo, 2011). Frequent exacerbations also accelerate the rate of lung function decline, which increases in a linear fashion as the number of exacerbations per year increase (Halpin, 2012).
9.3.2 Quality of Life

Acute exacerbations of COPD significantly impair patients’ health status. Different tools have been used to assess the effect of exacerbations on quality of life and all of these instruments show significant deterioration that persists for prolonged periods of time. Major recovery is seen four weeks after the event; however, it may take up to six months to achieve baseline functionality. If patients suffer another exacerbation during this time period, the effects on health status are much more profound (Semin­gual, 1998; Spencer, 2003).

An acute fall in outdoor activities is seen after an exacerbation. This reduction is thought to be related to physical inactivity, bed rest, and changes in metabolic, nutritional, and inflammatory states associated with the episode (Donaldson, 2005; Pitta, 2006). Exacerbations also have permanent effects on physical activity of the patients. Patients with frequent exacerbations (>2 per year) have a faster decline in time spent outdoors each day, -0.16 h/year, compared to infrequent exacerbators (Donaldson, 2005).

9.3.3 Mortality

Mortality after a severe exacerbation requiring hospitalization increases dramatically to 40 deaths per 10,000 patients per day in the first week after admission. The rate then gradually drops down to 5 deaths per 10,000 patients per day after 3 months (Suissa, 2012). There is a wide range of reported inpatient mortality from COPD exacerbations which is influenced by comorbid conditions and practice variations. Risk factors for inpatient mortality include cor pulmonale, congestive heart failure, low arterial pH, age, \( \text{SpO}_2 < 86\% \), mechanical ventilation, and low body mass index (Connors, 1996; Roberts, 2002).

Frequent acute exacerbations are independent risk factors for all-cause mortality in COPD (Soler-Cataluna, 2005). The risk of death increases with each subsequent exacerbation. The mortality risk is five times greater after the tenth admission compared to the first admission (Suissa, 2012).

9.3.4 Factors Associated with COPD Exacerbations

It is estimated that COPD patients suffer between one and four exacerbations per year; however, these events are not uniformly distributed among all individuals with COPD. Many factors have been identified to increase the risk and susceptibility to exacerbations. A list of known risk factors associated with repeated exacerbations is provided in Table 9.1. The single best predictor of a future exacerbation is a history of prior exacerbations. Exacerbations tend to occur more frequently as the disease progresses.
In the ECLIPSE cohort, other factors associated with frequent (≥ 2 per year) exacerbations were gastro-esophageal reflux, poorer quality of life, and elevated serum white blood cell count (Hurst, 2010).

COPD exacerbations tend to occur in clusters and the risk of subsequent exacerbations increases exponentially with each episode. After the 10th episode of exacerbation, the risk of subsequent exacerbations is 24-fold higher relative to the risk after the first episode (Suissa, 2012). A subset of patients experience exacerbations more frequently and are identified as the ‘frequent exacerbator’ phenotype. See section 9.4.5 for more information about this phenotype.

Table 9.1: Risk Factors associated with frequent exacerbations of COPD (Modified from: Miravitlles, 2012)

<table>
<thead>
<tr>
<th>Risk Factors</th>
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<tbody>
<tr>
<td>History of previous exacerbation</td>
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<tr>
<td>- Most predictive risk factor; odds ratio &gt;5</td>
</tr>
<tr>
<td>Older age</td>
</tr>
<tr>
<td>Asthma - COPD overlap syndrome OR COPD with bronchodilator responsiveness</td>
</tr>
<tr>
<td>Lower body mass index (BMI)</td>
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<tr>
<td>COPD severity:</td>
</tr>
<tr>
<td>- Greater baseline dyspnea</td>
</tr>
<tr>
<td>- Low FEV&lt;sub&gt;1&lt;/sub&gt;</td>
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<tr>
<td>- Low PaO&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>Inflammation</td>
</tr>
<tr>
<td>- Greater airway inflammation</td>
</tr>
<tr>
<td>- Greater systemic inflammation</td>
</tr>
<tr>
<td>Bacterial load in stable disease phase</td>
</tr>
<tr>
<td>Chronic bronchial hyper-secretion</td>
</tr>
<tr>
<td>Comorbidity/ extra pulmonary manifestations</td>
</tr>
<tr>
<td>- Cardiovascular</td>
</tr>
<tr>
<td>- Anxiety-depression</td>
</tr>
<tr>
<td>- Myopathy</td>
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<tr>
<td>- Reflux</td>
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</table>

FEV<sub>1</sub>: Forced expiratory volume in 1 second, PaO<sub>2</sub>: Partial pressure of oxygen in arterial blood.
9.4 COPD Phenotypes

A phenotype refers to the physical appearance or biochemical characteristics that result from the expression of genes, environmental influences, and their interactions. In COPD, the causative genes are mainly unknown or poorly characterized; hence, the phenotypes in COPD are synonymous with clinical subgroups. The one exception to this clinical characterization is alpha 1-antitrypsin (A1AT) deficiency where a defined genetic abnormality predisposes to the development and rapid acceleration of COPD. Classification of patients with different COPD phenotypes identifies subgroups of patients with features that impact their outcomes and response to certain treatments. Thus, COPD phenotype is defined as: “A COPD phenotype is a single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes (symptoms, exacerbations, response to therapy, rate of disease progression or death).” (Han, 2010)

The concept of COPD phenotypes dates back to the original recognition of smoking associated lung disease with two separate categories: emphysema and chronic bronchitis, which were clinically classified as the “pink puffer” and “blue bloater” (Burrows, 1964; Burrows, 1966). These were considered separate diseases before being unified under the term COPD (Karon, 1960). The heterogeneity in COPD has long been recognized (Warren, 2009) and suggestions of different phenotypes have also been described previously (Snider, 1989). One phenotype is unlikely to be uniquely present in a patient. As described by Snider in 1989, there seems to be significant overlap among subgroups where one patient may have multiple different phenotypic traits. Figure 9.3 shows a non-proportional Venn diagram of different COPD phenotypes.

9.4.1 Different Phenotypes of COPD

The phenotypes of COPD can be broadly categorized under the following types: genetic, physiologic, anatomic, and clinical. Table 9.2 is a list of various COPD phenotypes in these respective categories which are distinguished based on their disease manifestations, clinical course, and therapeutics.

9.4.2 Genetic: Alpha 1-antitrypsin Deficiency

Alpha 1-antitrypsin (A1AT) deficiency is the most common and most well established genetic cause of emphysema. A1AT is a serine proteinase inhibitor or serpin encoded on the serpin a-1 gene (Pi) on chromosome 14. Expression of two parental alleles determines the protein phenotype. Normal phenotype PiMM is present in 90% of the white population. There are more than 75 know pleomorphic alleles, some of them
Figure 9.3: Non-proportional Venn diagram of COPD phenotypes. The COPD subset is colored red. The grey rectangle represents airflow obstruction. The yellow subsets have features of either chronic bronchitis, emphysema, asthma or alpha 1-antitrypsin deficiency (A1ATD) but do not have airflow obstruction to qualify for COPD. Subset areas are non-proportional to the actual relative subset size. Patients with asthma whose airflow obstruction completely normalizes (subset 11) are not considered to have COPD. Because in many cases it is nearly impossible to differentiate patients with asthma whose airflow obstruction does not remit completely from persons with chronic bronchitis and emphysema who have airflow obstruction with bronchodilator responsiveness, patients with unremitting asthma are classified as having COPD, asthma - COPD overlap syndrome or COPD with bronchodilator responsiveness (subset 8, 9 & 10). Chronic bronchitis and emphysema with airflow obstruction usually occur together (subset 5), and some patients may have asthma associated with these two disorders (subset 9). Individuals with asthma who have been exposed to chronic irritation, such as from cigarette smoke, may develop a chronic productive cough, which is a feature of chronic bronchitis (subset 8). Persons with chronic bronchitis and/or emphysema without airflow obstruction (subsets 1, 2 & 3) are not classified as having COPD. A small proportion of patients with emphysema have A1ATD as a contributing etiology (subset 7). Not all patients with A1ATD develop COPD. Patients with airway obstruction due to disease with known etiology or specific pathology such as cystic fibrosis, bronchiectasis or obliterative bronchiolitis (subset 12) are not included in this definition. Modified from American thoracic Society (ATS), 1995.
### Table 9.2: Characteristics and therapeutic implications of different phenotypes of COPD

<table>
<thead>
<tr>
<th>GENETIC: Alpha 1-antitrypsin deficiency</th>
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<tbody>
<tr>
<td><strong>Clinical Course</strong></td>
<td>Early onset COPD</td>
</tr>
<tr>
<td></td>
<td>Familial tendency with variable penetrance</td>
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<tr>
<td></td>
<td>Increased susceptibility to smoking related lung injury</td>
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<tr>
<td></td>
<td>Emphysema can have variable anatomic distribution and lower lobe predominance</td>
</tr>
<tr>
<td><strong>Therapeutic Implications</strong></td>
<td>Augmentation therapy with intra-venous alpha 1-antitrypsin</td>
</tr>
</tbody>
</table>

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<tr>
<th>ANATOMIC: Emphysema predominant phenotype</th>
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<tbody>
<tr>
<td><strong>Clinical Course</strong></td>
<td>More dyspnea and exercise intolerance</td>
</tr>
<tr>
<td></td>
<td>Higher severity of airflow limitation and faster rate of lung function decline</td>
</tr>
<tr>
<td></td>
<td>Higher risk for exacerbations</td>
</tr>
<tr>
<td><strong>Therapeutic Implications</strong></td>
<td>Possibly more benefit from dual bronchodilator therapy and pulmonary rehabilitation in symptomatic patients</td>
</tr>
<tr>
<td></td>
<td><strong>Lung volume reduction surgery</strong>: consideration for upper zone predominant emphysema in patients with refractory poor function status</td>
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<tr>
<td></td>
<td><strong>Endobronchial valve</strong> (one way valves); consideration for heterogeneous emphysema with no collateral ventilation</td>
</tr>
<tr>
<td></td>
<td><strong>Endobronchial coils</strong>: consideration for heterogeneous or homogenous emphysema irrespective of collateral ventilation</td>
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<table>
<thead>
<tr>
<th>PHYSIOLOGICAL: Asthma - COPD overlap syndrome OR COPD with bronchodilator responsiveness</th>
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<tbody>
<tr>
<td><strong>Clinical Course</strong></td>
<td>Faster rate of lung function decline</td>
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<tr>
<td></td>
<td>Higher risk for exacerbations</td>
</tr>
<tr>
<td></td>
<td>Higher frequency of hospitalizations</td>
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<tr>
<td><strong>Therapeutic Implications</strong></td>
<td>More beneficial effects of inhaled corticosteroids</td>
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</tbody>
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<table>
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<tr>
<th>CLINICAL: Frequent exacerbator phenotype (&gt; 2 acute exacerbations / year)</th>
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<tbody>
<tr>
<td><strong>Clinical Course</strong></td>
<td>Faster rate of lung function decline</td>
</tr>
<tr>
<td></td>
<td>More hospitalizations and utilization of health care cost</td>
</tr>
<tr>
<td></td>
<td>Higher risk of death</td>
</tr>
<tr>
<td><strong>Therapeutic Implications</strong></td>
<td>Medications to reduce inflammation: inhaled corticosteroids, long term macrolide (Azithromycin), phosphodiesterase 4 inhibitor (Roflumilast)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CLINICAL: Chronic bronchitis predominant type OR mucous secretor phenotype</th>
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<tbody>
<tr>
<td><strong>Clinical Course</strong></td>
<td>Higher risk and frequency of exacerbations</td>
</tr>
<tr>
<td></td>
<td>Faster rate of lung function decline</td>
</tr>
<tr>
<td><strong>Therapeutic Implications</strong></td>
<td>Phosphodiesterase 4 inhibitor (Roflumilast) reduces frequency of exacerbations</td>
</tr>
</tbody>
</table>
9.4.2.1 Therapeutic Implications

Augmentation therapy with plasma-derived A1AT is widely accepted and recommended in moderate to severe disease (Stockley, 2014). In randomized controlled trials, augmentation therapy slows down the rate of decline of lung density which is a marker of emphysema (Campos, 2014).

9.4.3 Anatomic: Emphysema-Hyperinflation Phenotype

Emphysema is the permanent destruction of the air spaces beyond the terminal bronchioles. The loss of elastic recoil and presence of expiratory flow limitation causes air-trapping and hyperinflation. The presence, severity, and distribution of emphysema is variable among individuals with COPD. This clinical phenotype is characterized by physiologic derangements that cause hyperinflation and air-trapping and are measured by low inspiratory capacity/total lung capacity ratio (IC/TLC <0.25), presence of emphysema on HRCT, and/or low diffusing capacity (DLCO).

Recently genetic associations have also been identified in the anatomic distribution and severity of emphysema. Mid-upper zone emphysema in smokers is linked with rs1980057 near HHIP and severe emphysema with rs8034191 on chromosome 15 (Castaldi, 2014). AAT deficiency is associated with lower zone predominant panacinar emphysema (Stockley, 2014).

Emphysema-hyperinflation rather than the severity of airflow obstruction is more closely associated with clinical symptoms of dyspnea and exercise intolerance (Diaz, 2000; O’Donnell, 2001). Identification of this phenotype is clinically important as dyspnea, exercise intolerance, and hyperinflation are independent predictors of mortality (Casanova, 2005; Martinez, 2006; Nishimura, 2002; O’Donnell, 1993). Patients with IC/TLC <0.25 (markers of hyperinflation) are more than three times more likely to die than those with higher IC/TLC ratios, regardless of FEV₁, age, dyspnea, exercise capacity, or comorbidities (Casanova, 2005). The presence of emphysema is also associated with the severity of airflow limitation and a faster rate of FEV₁ decline (Nishimura, 2012; Vestbo, 2011) and is an independent risk factor for increased frequency of COPD exacerbations (Han, 2011).

9.4.3.1 Therapeutic Implications

Hyperinflation, to a certain degree, is potentially reversible with appropriate treatments as evidenced by reductions in lung volumes after treatment with bronchodilators (Man, 2004; O’Donnell, 2004a). Dual bronchodilator therapies improve dyspnea and quality of life in symptomatic patients with emphysema-hyperinflation (Rabe, 2008; van Noord, 2005). Since they have more dyspnea and exercise intolerance, these patients are also expected to obtain greater benefit from pulmonary rehabilitation (Casaburi, 2009).
Patients with emphysema who maintain poor functional capacity despite maximal medical treatment and pulmonary rehabilitation can be candidates for lung volume reduction interventions to reduce the residual air trapped in the chest cavity and improve pulmonary mechanics and gas exchange. The National Emphysema Treatment Trial (NETT) showed that lung volume reduction surgery in patients with heterogeneously distributed upper zone predominant emphysema leads to improvement in functional capacity and a reduction in exacerbations and mortality (Fishman, 2003; Washko, 2008). Other less invasive options for lung volume reduction are placement of endo-bronchial coils and one way endo-bronchial valves. Appropriate candidates for endo-bronchial valves are patients with heterogeneous distribution of emphysema with no collateral ventilation to the emphysematous lobe or segment. Endo-bronchial coils, on the other hand, have been used in patients with homogenous and heterogeneous distribution of emphysema irrespective of collateral ventilation (Ninane, 2012; Sciurba, 2010; Shah, 2013).

9.4.4 Physiologic: Bronchodilator Responsive/ COPD-Asthma Overlap Syndrome

A subset of patients with COPD manifest significant responses to bronchodilators; however, this responsiveness does not produce normal lung function. The airways of these patients manifest chronic inflammation with both neutrophilic and eosinophilic cell infiltrations. This phenotype has been categorized as mixed asthma-COPD or COPD-asthma overlap syndrome (CAOS). Between 20–40% of COPD patients may have mixed CAOS (Miravitlles, 2012). Patients with CAOS experience a faster rate of decline in FEV$_1$ (Vestbo, 2011), higher risk for exacerbations, increased frequency of hospitalizations, and worse health related quality of life (Hardin, 2011; Menezes, 2014). The response to bronchodilators in patients with COPD is not longitudinally consistent; therefore, it may not be a reliable marker to identify a distinct phenotype (Albert, 2012). Sputum eosinophils and inhaled nitric oxide levels may be some of the features that can help identify CAOS. Other characteristics may include a history of asthma and/or atopy, frequent exacerbations, and wheezing.

9.4.4.1 Therapeutic Implications

Many large clinical trials of COPD and asthma have excluded this subset of patients as they are not exclusively classified as either asthma or COPD (Calverley, 2007). COPD patients that demonstrate even partial responsiveness (less than the American Thoracic Society criteria of >200 ml and >12% increase in either FEV$_1$ or FVC) have greater eosinophilic bronchial inflammation compared to non-responding patients (Papi, 2000). Several studies have used greater airflow reversibility (Kerstjens, 1993; Lee, 2010), a higher concentration of eosinophils in sputum (Brightling, 2005; Leigh, 2006), or a greater concentration of inhaled nitric oxide (Kunisaki, 2008; Lehtimaki,
2010) as markers of potential benefit in lung function and clinical symptoms after inhaled corticosteroids (ICS) treatment. ICS dose adjustments according to sputum eosinophil count have reduced hospitalizations and exacerbation frequency. When treated with LABA and ICS combination inhalers, CAOS patients have greater short and long term improvement in lung function compared with patients with emphysema who do not respond to bronchodilators (Lee, 2010; Mahler, 2002).

9.4.5 Clinical Frequent Exacerbator

In the recent years, much attention has been attracted by a subset of patients having frequent exacerbations of COPD. In longitudinal studies, some patients are more likely to develop exacerbations irrespective of their disease severity. Patients who suffer from two or more exacerbations a year maintain an increased propensity toward frequent exacerbations over the subsequent years, making them a consistent phenotype called ‘frequent exacerbators’. In the ECLIPSE study, which included 2138 patients with moderate-severe COPD, 12% of cases had ≥ 2 exacerbations per year over the 3-year course of the study. The frequent exacerbators maintained a notable stability over time. Of the patients suffering ≥ 2 exacerbations in first year, 60% had frequent exacerbations in the second year and 70% of the second year frequent exacerbators had frequent exacerbations in the third year (Hurst, 2010).

COPD exacerbation heterogeneity and susceptibility are likely caused by multiple contributing factors with complex interactions, as shown in Figure 9.4. Potential contributing factors include background airway and systemic inflammation, airway microbial patterns, host immunologic response, comorbid health conditions, genetic predisposition, viral and bacterial infections, and adherence to medications (Wedzicha, 2013).

The ‘frequent exacerbator phenotype’ has sparked great interest in recent years due to faster lung function decline, poor quality of life, and higher health care utilization and mortality within this group. See section 9.3 for more information on factors associated with frequent exacerbations and role of frequent exacerbations on lung function decline, health quality, and mortality. The current COPD treatment guidelines, therefore, encourage physicians to recognize ‘frequent exacerbators’, defined as those who have either two of more exacerbations per year or having one severe exacerbation in a year requiring hospitalization (GOLD, 2014).

9.4.5.1 Therapeutic Implications

The therapeutic goal for frequent exacerbators is to reduce the frequency of exacerbations, delay the next acute exacerbation, and minimize health care utilization and cost by reducing the severity of these episodes. Long acting bronchodilators like tiotropium have been shown to reduce the frequency of exacerbations (Vogelmeier,
Treatment modalities that reduce airway inflammation and have immune modulatory effects have been used successfully. For recurrent exacerbations, all current practice guidelines recommend addition of inhaled corticosteroids along with the bronchodilators. Inhaled corticosteroids reduce the frequency of exacerbations significantly and also improve health related quality of life in these individuals (ATS, 1995; GOLD, 2014).

Macrolides administered for a prolonged amount of time, such as azithromycin 250 mg daily, can be used as additional therapy to reduce exacerbation frequency (Albert, 2011). The potential for cardiotoxicity and hearing loss have to be cautiously monitored. Also, the risk of possible development of bacterial antibiotic resistance should also be considered. Roflumilast, an orally administered selective phosphodiesterase IV inhibitor, has anti-inflammatory effects. It has been approved for preventing exacerbations in patients with severe COPD and features of chronic bronchitis (mucous producers) (Calverley, 2009). In a recent large clinical trial, long term use of statins (simvastatin) did not reduce the number of acute exacerbations of COPD (Criner, 2014).

Figure 9.4: Schematic illustration of the frequent exacerbation phenotype. While many patients with COPD experience exacerbations, there is a subgroup of patients who enter a destructive cycle of frequent exacerbations with associated poorer outcomes. This phenotype of frequent exacerbators is maintained over time. Modified from Wedzicha, 2013.
9.4.6 Clinical: Chronic Bronchitis/Mucous Producer

Another COPD phenotype is chronic bronchitis, which is characterized by chronic cough and sputum expectoration. These patients demonstrate greater airway inflammation and a higher risk of respiratory infections (Prescott, 1995). Patients with this phenotype have a higher risk of COPD exacerbations, independent of other known risk factors (Foreman, 2007; Miravitlles, 2011). Some studies have also described an association with faster FEV$_1$ decline, particularly in younger adults (Guerra, 2009).

9.4.6.1 Therapeutic Implications

The most important clinical characteristic of the chronic bronchitis/mucous producer phenotype is the predisposition to frequent recurrent exacerbations. Phosphodiesterase-4 inhibitors such as roflumilast produce greater reductions in COPD exacerbation frequency in patients with this phenotype compared to those who do not produce mucous (Calverley, 2009).

9.5 Gender Differences in COPD

In the past few decades the prevalence and mortality from COPD have increased rapidly in women compared with men which has changed the historic perspective that COPD is predominantly a disease of men. It is thought that the increase in the prevalence of cigarette smoking among women is the major contributor to this epidemiological shift. Gender differences are also observed in susceptibility to the development of COPD from tobacco exposure, clinical features, response to certain treatments, and health care utilization. Table 9.3 provides a summary of the gender differences in COPD.

9.5.1 Reasons for Gender Differences in COPD

It is commonly believed that behavioral and environmental factors are responsible for the gender disparities in COPD. However, there is also growing evidence of gender-based genetic and hormonal factors playing an important role in this regard.

9.5.1.1 Change in Tobacco Consumption Trend

As mentioned previously, cigarette smoking is the most influential risk factor for COPD development and progression in the developed world. Trends in COPD mirror the trends in cigarette smoking in populations. The risk of COPD development from cigarette smoking increased throughout last century in the US as successive genera-
tions began smoking at earlier ages. Daily cigarette consumption in the US peaked during the 1970s in males, whereas the peak among female smokers did not occur until the 1980s (Burns, 2003). In developing countries, the prevalence of cigarette smoking is still rising. By 2025, the prevalence of smoking among females is predicted to increase to 20% from 9% in the early 2000s (Mackay, 2003).

9.5.1.2 Tobacco Susceptibility
There is mixed evidence suggesting gender differences in the susceptibility to the development of COPD caused by smoking. Women tend to develop severe COPD with lower cumulative cigarette exposure, and at a younger age, than men. They also demonstrate a faster rate of FEV₁ decline (Gan, 2006). The gender difference is more profound in earlier disease phases where women seem to have more airflow obstruction with less (<20 pack years) cumulative smoking exposure. With higher smoking exposures and in later phases of the disease, gender disparities become less obvious (Sorheim, 2010). The greater susceptibility to cigarette smoke in women could be due to women having smaller airways; consequently, the same amount of smoking will lead to relatively higher exposure. Other smoking behaviors such as inhalation techniques may also play a role (Han, 2007). Gender related genetic differences also disproportionately increase the risk in women. In one observational study, a smoking female who has first-degree relatives with early-onset COPD is almost twice as likely to experience airflow obstruction, and 3.5 times more likely to have severe obstruction (FEV₁ < 40% predicted) than male relatives who smoked (Silverman, 2000).

9.5.1.3 Biologic Differences
Female sex hormones are known to influence airway function, especially in asthma (Han, 2007). The increased susceptibility in women may start in early childhood. A larger reduction in lung function is seen in girls than boys when exposed to tobacco smoke or environmental air pollution (Chen, 2005; Rojas-Martinez, 2007). Based upon epidemiologic studies, up to 23% of all COPD patients have not been exposed to tobacco smoke (Lamprecht, 2011). Nearly 80% of these patients are females, suggesting that women are more vulnerable to non-smoking related COPD risk factors (Birring, 2002). Variations in immune responses are also observed between males and females with COPD. Males tend to have higher levels of interlukin-6 and vascular endothelial growth factor which may suggest higher emphysema predominance in males. Females have relatively higher levels of interlukin-16. It is unclear how these differences play a role in disease course (de Torres, 2011).
Table 9.3: Gender differences in Chronic Obstructive Pulmonary Disease (COPD)

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epidemiology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence</td>
<td>Higher by administrative data</td>
<td>Higher by self-report; higher than males in developed world; increasing in developing world</td>
</tr>
<tr>
<td>Mortality</td>
<td>Declining during past few decades</td>
<td>Stable over past few decades</td>
</tr>
<tr>
<td><strong>Risk Factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tobacco use</td>
<td>Peaked during 1970s in USA</td>
<td>Peaked during 1980's in USA; increasing in developing world</td>
</tr>
<tr>
<td>Tobacco susceptibility</td>
<td>Susceptible</td>
<td>More susceptible</td>
</tr>
<tr>
<td>Environmental risks</td>
<td>Air pollution; occupational exposures</td>
<td>Increasing occupational exposures; indoor air pollution major risk in developing world</td>
</tr>
<tr>
<td>Phenotypic factors</td>
<td>More emphysema; bronchial hyperresponsive and correlates with atopy</td>
<td>More chronic bronchitis; more hyperresponsiveness and correlates with smoking</td>
</tr>
<tr>
<td><strong>Clinical Features</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>Correlate with disease activity</td>
<td>More and higher intensity dyspnea; less phlegm</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>IHD, arrhythmias, alcoholism, renal failure, cancers</td>
<td>Depression, anxiety, osteoporosis, reflux, IBD</td>
</tr>
<tr>
<td>Acute exacerbations</td>
<td>Higher associated mortality; more number of hospitalizations</td>
<td>Lower associated mortality</td>
</tr>
<tr>
<td><strong>Treatment options</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking cessation</td>
<td>More attempts and more sustained quitting; nicotine replacement more effective</td>
<td>Fewer attempts and less sustained quitting; better improvement in FEV₁ after quitting</td>
</tr>
<tr>
<td>Pharmacologic treatment</td>
<td>ICS reduces phlegm; benefits of LTOT may not be as good as women; Inhaler use may be better</td>
<td>ICS may not reduce phlegm but worsened deterioration on stopping; chronic macrolide therapy may be more effective</td>
</tr>
<tr>
<td>Pulmonary rehabilitation</td>
<td>Effects may be more sustained</td>
<td>More emotional and psychosocial benefits</td>
</tr>
</tbody>
</table>
The assessment of COPD prevalence has either relied on self-reports of disease, spirometric analysis, or medical billing. Women tend to have a higher prevalence of COPD compared to men by self-report, whereas men have a higher prevalence when medical billing data are used (Camp, 2007). In the US, the prevalence of moderate COPD measured by spirometry increased in women from 50.8 to 58.2 per 1000 from 1975 (NHANES I) to 2000 (NHANES III). The prevalence in men decreased from 108.1 to 74.3 per 1000 during the same period. Self-reported prevalence of COPD from 1999–2008 has remained higher in women than men (Mannino, 2002). Similar trends are noted in other developed countries (Bischoff, 2009; Gershon, 2010). In developing countries, COPD prevalence is still higher in men than women but is expected to rise in women given changes in smoking trends and air pollution (Bhome, 2012; Menezes, 2005; Schirnhofer, 2007).

A recent comprehensive assessment of smoking related mortality in the US showed that in the decade from 2000 to 2010, male and female current smokers had similar relative mortality risks from COPD, 26.6 for males and 22.3 for females. This risk was doubled compared with the period of 1982–1988 (Thun, 2013). For the first time in 2000, the total number of female deaths from COPD surpassed the number of male deaths because the percentage of women in the general U.S population was greater. The age-adjusted COPD death rates for men were 1.3 times more than for women (Mannino, 2002).

### 9.5.3 Clinical Features and Phenotypic Differences

Numerous studies highlight the gender differences in clinical presentation and disease course. Women are more likely to report dyspnea and a higher severity of dyspnea compared to men with comparable smoking exposure and FEV₁ (de Torres, 2013).
Men are more likely to report productive cough than women (Cydulka, 2005; Gershon, 2010). These differences may be due to behavioral and societal influences where women are less likely to report phlegm production or dyspnea than men (Becklake, 1999; Camp, 2007).

In the ECLIPSE study, no difference was seen in the ages of males and females for a given GOLD category. However, for each GOLD category, women had lower BMI, less smoking exposure, and reported more exacerbations than men (Agusti, 2010). Higher exacerbation rates among women also occurred in the TORCH study (Celli, 2011).

Gender differences are also observed in COPD phenotypes. Based on National Health Interview Survey data, chronic bronchitis is more common in women whereas emphysema is more common in men. Radiographic and histological data also suggest that women with COPD tend to have smaller airway lumens with thicker bronchial walls and less severe peripheral emphysema than men (Dransfield, 2007).

### 9.5.4 Comorbidities

Comorbid diseases are commonly present in patients with COPD; however, their prevalence differs in males and females. Cardiovascular comorbidities, arrhythmias, ischemic heart disease, and cancers are more often seen in male patients with COPD compared to females (Agusti, 2010; Almagro, 2010). Women have higher rates of osteoporosis, diabetes, inflammatory bowel disease, anxiety, and depression (Agusti, 2010; Almagro, 2010; Gudmundsson, 2005).

### 9.5.5 Treatment Disparities

Smoking cessation is critical in COPD management. Mixed results have been observed in studies between men and women. Some analyses suggest that women have lower smoking cessation success rates and tend to quit less frequently (Han, 2007). A recent large population study from the US, Canada, and UK found little gender differences in smoking cessation (Jarvis, 2013). Certain pharmacotherapies like bupropion and varenicline seem to have better results in women, whereas, nicotine replacement therapy has shown better success rates in men (Han, 2007). Women experience a 2.5 fold greater improvement in lung function (FEV$_1$) after smoking cessation than men (Scanlon, 2000).

Bronchodilators and inhaled corticosteroids have remained the cornerstone of COPD management for many years. Studies suggest similar efficacy of inhaled salmeterol/fluticasone combination therapy and tiotropium in both genders in terms of FEV$_1$, exacerbation rate, and quality of life (O’Donnell, 2004; Vestbo, 2004). Mixed findings have been noted in medication adherence. In one study with mild-moderate COPD patients, the proportion of females on respiratory medicines was twice that of
men. However, in severe COPD, no gender differences in prescriptions were noted (Dales, 2006). Men are reported to be more likely to be on newer dry powder inhalers rather than metered dose inhalers (Sestini, 2006). Disproportionately lower rates of influenza and pneumonia vaccine usage in women have also been reported (Wershof Schwartz, 2013).

9.5.6 Health Care Delivery

Despite substantial increases in prevalence and mortality from COPD among females, health care providers remain more likely to diagnose males with COPD than females. In a study done in the US and Canada, physicians were found more likely to diagnose females with asthma and males with COPD in similar hypothetical cases. The bias decreased if spirometry values were provided to the physicians (Chapman, 2001). Similar results were seen in a subsequent study in Spain (Miravitlles, 2006). In another large population study, women were 1.27 times more likely to have under-diagnosed COPD despite spirometric values confirming the presence of airflow limitation (Ancochea, 2013). Women are more likely to report delay in COPD diagnosis, difficulty in reaching physicians, and spending insufficient time with their physician (Martinez, 2012).

9.6 Conclusion

The natural disease course of COPD is generally characterized by an accelerated decline in lung function. However the rate of decline remains highly variable among individuals and is influenced by numerous factors. Smoking exposure impairs lung growth, reduces maximal lung function and accelerates the rate of deterioration. Smoking cessation at any stage of the disease slows the rate of decline. Exacerbations punctuate the disease course and increase the risk of mortality, morbidity and health care utilization. COPD can be classified into different phenotypes based on certain features that are responsible for clinical variations in the disease course and outcomes among individuals. Some of the well-recognized phenotypes are frequent exacerbators, alpha 1-antitrypin deficiency, emphysema predominant, COPD-asthma overlap syndrome, and mucous producers. Gender differences in the epidemiology of COPD are primarily implicated to the changing smoking trends. Women also appear to be more susceptible to smoking related lung injury and tend to have slightly different clinical features and outcomes than men.
9.7 Summary Points

1. The disease course of COPD is classically characterized by accelerated lung function decline. The rate of this decline, however, is highly variable among individuals.
2. Factors that are associated with a faster rate of decline include active smoking, genetic susceptibility, emphysema, broncho-reactivity and early disease.
3. Acute exacerbations of COPD have short and long term effects on disease course and outcomes. They are associated with increased health care utilization and costs, decline in lung function and life quality and an increase in mortality.
4. Many factors increase the risk and susceptibility to exacerbations. The single most important risk factor is a prior history of a recent exacerbation.
5. COPD phenotypes are disease attributes that describe differences between individuals with COPD as they relate to symptoms, exacerbations, response to therapy and rate of disease progression.
6. Well recognized COPD phenotypes are alpha 1-antitrypsin deficiency, emphysema predominant, COPD-asthma overlap syndrome, frequent exacerbator and chronic bronchitis. Each of these phenotypes has different therapeutic implications in patient management.
7. In the developed world, gender differences in the epidemiologic trends of COPD are primarily attributed to the change in smoking behavior in men and women over the past several decades.
8. Women tend to have an increased susceptibility to smoking related lung damage, report more dyspnea, and experience more diagnostic delays compared with men with COPD.

References


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10 COPD Is a Multi-Organ Disorder: Systemic Manifestations

Key Points
1. COPD is a disorder that affects multiple systems beyond the lungs; these non-pulmonary manifestations include cardio- and cerebrovascular, oncologic, musculoskeletal, hematologic, psychological, and endocrine effects.
2. Much of the early mortality related to COPD is caused by cardiac and oncologic effects of COPD; late mortality is caused by respiratory failure.
3. Significant COPD-related morbidity is due to nonpulmonary manifestations.
4. In general, management of the extra-pulmonary manifestations of COPD is the same as treatment of these processes when they are not associated with COPD.
5. It remains to be determined if treatment of COPD ameliorates its nonpulmonary manifestations and whether management of COPD’s extrapulmonary processes improves the health and wellbeing of individuals with COPD.

10.1 Introduction

Although COPD is usually defined and managed as a disorder confined to the lungs, numerous investigations over the past decade have demonstrated that COPD is associated with multiple nonpulmonary manifestations that contribute significantly to its morbidity and mortality. These associated processes include cardiac and cerebrovascular, oncologic, musculoskeletal, hematologic, psychological, and endocrine effects (Cavailles, 2013; Albu, 2012; Huertas, 2011; Nussbaumer-Ochsner, 2011; Barnes, 2009; Decramer, 2008; Augusti 2007; Augusti, 2008; Fabbri, 2008).

10.2 Inflammation in COPD

The pathophysiologic process linking pulmonary and nonpulmonary manifestations of COPD has been postulated to be inflammation. For a detailed review of the pathogenesis of pulmonary and systemic inflammation in COPD, please see chapter 6, Pathogenesis of COPD.

10.3 COPD Mortality

As discussed in Chapter 9, Natural History of COPD, Phenotypes, and Gender Differences in COPD, the major causes of death in individuals with early COPD (measured
by severity of airflow limitation (AFL) are lung cancer and cardiac disease (Sin, 2006; Mannino, 2006). During acute exacerbations of COPD, the leading causes of death are heart failure (37.2%), pneumonia (27.9%), pulmonary (20.9%), and respiratory failure (14%) (Zvezdin, 2009). Even when adjusted for sex and smoking history, individuals with AFL have an increased risk for acute myocardial infarction, hazard ratio (HR) 3.53 [95% confidence interval, 3.02–4.13] and for stroke, HR 2.79 [2.56–3.04] (Feary, 2010). For individuals aged 35–44 years old, the risk is even greater, acute myocardial infarction, HR 10.34 [3.28–32.60] and stroke, HR 3.44 [0.85–13.84] (Feary, 2010).

A 17 year longitudinal study of mortality among patients with COPD from 1987 to 2004 who were started on long term oxygen in Sweden showed that 71% of patients died of respiratory causes, 16% circulatory processes, and 7.6% from cancer (Ekstrom, 2011). However, the adjusted annual change in mortality due to COPD declined by 3.0% annually whereas nonrespiratory causes of death rose by 6.3% annually. Another Swedish longitudinal study of 21,361 patients diagnosed with COPD from 1999 to 2009 showed that the number of COPD exacerbations declined from 3.0 to 1.3 exacerbations/patient/year and the number of hospitalizations decreased from 1.02 to 0.2 per patient per year (Stallberg, 2014). Long acting anti-cholinergic and inhaled corticosteroid/long acting beta agonist prescriptions increased from 0% to 36% and 37% of patients, respectively (Stallberg, 2014). Thus, respiratory morbidity and mortality among those with COPD are declining but nonrespiratory morbidity and mortality are increasing. These improvements in respiratory mortality may be due to better pharmacologic and nonpharmacologic management of COPD. The increase in nonrespiratory related mortality suggests that greater identification and management of nonpulmonary processes associated with COPD may be warranted to improve the longevity and health of individuals with COPD.

10.4 Cardio- and Cerebral-vascular Disease

The prevalence of cardiovascular (CV) disease in individuals with COPD, 20–22%, is over two-fold greater than in the general population who do not have COPD, 9% (Mannino, 2008). Among patients with AFL, the prevalence of cardiovascular disease is increased over 2 fold (odds ratio (OR) = 2.7, 95% CI 2.3–3.2) (Finkelstein, 2009). Reduced FEV₁ is associated with increased CV mortality independent of age, gender, and smoking history (Sin, 2005A). Adjusted CV mortality rises by 28% for every 10% decrease in FEV₁ (Sin, 2005B). Coronary artery calcifications detected by CT scanning were increased in individuals with COPD compared with smokers with normal spirometry or nonsmokers and correlated with dyspnea, exercise capacity, all cause mortality, and inflammatory markers (IL6, IL8, CCP 16, SP D, and neutrophils) but not FEV₁ or acute exacerbations of COPD (Williams, 2014).

Acute COPD exacerbations are associated with an increased rate of myocardial infarction. Elevated cardiac enzymes occur in 17–27% of patients hospitalized for
COPD exacerbations and MI occurs in 1:12 patients (McAllister, 2012). There is a 2.27 fold increase in MI during the 5 days after onset of a COPD exacerbation (Donaldson, 2010). Acute COPD exacerbations may increase the risk of cardiac ischemia and infarction through demand ischemia, acute coronary syndrome with plaque rupture, peripheral arterial stiffness, interactions between the heart and lungs including increased right and left ventricular afterload due to increased intrathoracic pressures, medication effects, and cardiac muscle mass depletion (Harvey, 2014; Visca, 2013).

β blockers significantly decrease mortality after myocardial infarction in patients with COPD (Quint, 2013). Of 1063 patients with COPD presenting with an initial MI from 2003–2008, the mortality HR was 0.59 [95% confidence interval (CI), 0.44–0.79] for those who were taking β blockers at presentation and 0.50 [95% CI, 0.36–0.69] for those who started β blockers during that admission (Quint, 2013). β blockers are tolerated well by patients with all stages of COPD including individuals who demonstrated bronchodilator responsivity during spirometry testing (Salpeter 2002, 2003, 2004, 2005).

10.4.1 Heart Failure

Approximately 19–48% of patients with heart failure have COPD and 9–52% of patients with COPD have heart failure (Hawkins, 2009). The relative risk of developing heart failure among patients with COPD is 4.5 controlling for age and cardiovascular risk factors. Coexistent COPD and heart failure is associated with greater mortality and healthcare utilization than either disorder alone (Hawkins, 2013).

It may be difficult to distinguish COPD and heart failure because the symptoms frequently overlap and include nonspecific features such as exertional dyspnea, fatigue, and reduced activity. The presence of lower extremity edema may be due to cor pulmonale or left ventricular failure. Emphysematous changes may mask the presentation of pulmonary edema on chest radiographs and it may be difficult to determine heart size. Echocardiography may be technically difficult in patients with COPD due to hyperinflation and attenuation of the ultrasound signal. Minor elevations in B-type natriuretic peptide (BNP) may be nonspecific and due to cor pulmonale, pulmonary hypertension, left, right, or biventricular failure. A BNP greater than 400 pg/ml suggests left ventricular failure and warrants evaluation of LV function with an ECHO. Finally, use of inhaled bronchodilators in patients who have heart failure but do not have COPD is associated with a 69% increase in mechanical ventilation and a 40% increase in intravenous vasodilator use (Singer, 2008).

Most pharmacologic treatment trials of respiratory medications for COPD have excluded concomitant heart failure. Chronic β blocker use in individuals with COPD and CHF is considered to be safe and β blockers can be continued during hospitalizations for COPD exacerbations (Stefan, 2012). Statins, ACE inhibitors, and angiotensin receptor blockers reduce respiratory related hospitalizations among individuals with COPD.
Lung Cancer

COPD (Mancini, 2006) and statin and ACE inhibitor use at the time of admission is associated with a reduction in mortality (Mortenson, 2009). In contrast, patients with left ventricular heart failure who are treated with β agonists have increased mortality and hospitalization (Au, 2003). The use of systemic steroids (more than 20 mg/d of prednisone) increases the risk of heart failure decompensation (Souverein, 2004) and phosphodiesterase inhibitors are associated with an increased risk of dysrhythmias (Barnes, 2013). There is an increasing need to assess and determine the optimal management of COPD in individuals who also have heart failure (Hawkins, 2009, 2011, 2013; Mentz, 2012).

10.5 Lung Cancer

Of 100 smokers, approximately 20 will develop COPD, and, of those 20 individuals, 5 will develop lung cancer whereas of the 80 smokers who do not develop COPD, only 5 will develop lung cancer (Young, 2009). Thus, the risk of lung cancer is significantly greater in smokers with COPD, 1:4, compared with smokers who do not have COPD, 1:16. (Figure 10.1) The relative risk of lung cancer in individuals with a diagnosis of COPD is 2.22 [1.66–2.97], chronic bronchitis 1.52 [1.25–1.84], and emphysema 2.04 [1.72–2.41] (Brenner, 2011). The visual detection of emphysema on CT scans increases the odds ratio for lung cancer, 3.5 [2.71–4.51] (Smith, 2012).

Between 50% and 90% of all lung cancer patients have COPD (deTorres, 2007; Turner, 2007; Wilson, 2008; Young, 2009). COPD is associated with a 2 to 6-fold increase in lung cancer risk compared with smokers who do not develop COPD (deTorres, 2007, 2011; Mannino, 2003; Turner, 2007; Wilson, 2008; Young, 2009). AFL increases the risk of lung cancer independent of the smoking history (Wilson, 2008). Several studies have found that the risk of lung cancer is greater in individuals with mild to moderate AFL compared to those with more severe COPD (Young, 2009;
Anthonisen, 2005; deTorres, 2011); whereas others have found that the lung cancer risk increases with the decline in lung function (Mannino, 2003). The presence of COPD portends a worse prognosis for individuals with lung cancer (Kiri, 2010). Thus, not only is the risk for lung cancer greater for smokers who develop AFL, they generally do worse.

### 10.5.1 Pathogenetic Links Between COPD and Lung Cancer

The strong association between lung cancer and COPD has spurred studies to discover common cellular and molecular pathways for these two processes (Houghton, 2013; Adcock, 2011; Yang, 2011; Young, 2011). Inhalation of tobacco smoke in genetically susceptible individuals may generate inflammation and reactive oxygen species within the lungs and systemically (El-Zein, 2012). These inflammatory cytokines and reactive biochemical compounds may induce or repress gene expression and cause alterations in genetic and epigenetic complexes leading to deranged cellular proliferation and altered lung airway and parenchymal anatomy and function (Lee, 2009). Other recently discovered biologic pathways are also common to the development of COPD and lung cancer. MicroRNA’s modulate post-translational gene regulation and are critical for lung development, pulmonary inflammation, and the development of bronchogenic carcinoma (Sittka, 2013). The biologic processes maintaining telomeres, the DNA-protein caps on the ends of chromosomes, have also been implicated in the pathogenesis of several pulmonary processes including idiopathic pulmonary fibrosis, COPD, and lung cancer and may be another common pathway that is deranged in these disorders (Ganser, 2013). Unifying pathogenetic processes for COPD and lung cancer are being intensely investigated to identify common pathways and means to interdict the development of both of these disorders.

### 10.5.2 Lung Cancer Screening

Based upon the American National Lung Screening Trial that demonstrated a 20% reduction in lung cancer mortality in the group that underwent low dose CT scan screening examinations, current recommendations advise lung cancer screening for smokers or former smokers with at least 30 pack years smoking history and age between 55 and 74 years (The National Lung Screening Trial Research Team, 2011; Wender, 2013). Although lung cancer screening has not been recommended for individuals with COPD, based upon the results of the NLST, low dose chest CT scanning screening may be beneficial for individuals with COPD, even with moderate AFL. Earlier detection of AFL and diagnosis of COPD may identify individuals with even greater potential benefit from lung cancer screening (Sekine, 2012).
10.5.3 Management of Lung Cancer

Multiple clinical practice guidelines for lung cancer have been published (von Dincklage, 2013). Evaluation and management of suspected lung cancer in a patient with COPD begins with radiographic and cardiopulmonary physiologic assessments (Backhus, 2013). In general, once the histopathological diagnosis is confirmed or the clinical suspicion for lung cancer is sufficiently high, the critical decision is to determine whether the patient is a candidate for surgical excision of the cancer. Only 15–25% of lung cancers are operable at the time of diagnosis (Von Groote-Bidlingmaier, 2011). Essential components for the determination of a patient’s candidacy for surgical resection of bronchogenic carcinoma include radiographic staging of the cancer and assessment of cardiovascular and pulmonary physiologic function. Because of the high prevalence of coronary artery disease among individuals with COPD, ascertainment of the cardiovascular risk for anesthesia and thoracic surgery should be pursued. If either the FEV$_1$ or DLCO are less than 80% of predicted, the postoperative lung function should be calculated by either quantitative perfusion scans or the anatomic method based upon the number of lung segments to be resected. If either the FEV$_1$ or DLCO % predicted is less than 40%, the patient is at increased risk for perioperative respiratory complications including death, infections, respiratory compromise or failure, and requirement for supplemental oxygen. In patients with marginal pulmonary physiologic function, cardiopulmonary exercise testing demonstrating a maximal oxygen consumption (VO$_2$ max) less than 15 ml/kg/min precludes surgery (Colice, 2007). Combined lung volume reduction surgery and lung cancer surgical resection in a selective population of patients with emphysema in a upper zone predominant distribution and cancer stage amenable to resection may improve postoperative lung function and respiratory symptoms as well as permit resection in patients who might otherwise not be considered for surgery (Choong, 2009; Colice, 2007).

Historically, the most common lung cancer subtype among male smokers was squamous cell carcinoma but more recent studies show that by the mid 1990’s adenocarcinoma was the most frequent histopathologic subtype regardless of gender or smoking history (Devesa, 2005).

Surgery is the first line treatment for lung cancer depending upon stage and surgical and operative risk factors. For patients with nonresectable lung cancer, chemotherapy, radiation therapy, or combination therapy may be pursued after referral to oncologists and radiation specialists.

Pulmonary rehabilitation may benefit patients with lung cancer and COPD by improving quality of life, performance status, oxygen consumption, exercise tolerance, chemotherapy-associated fatigue, and perioperative morbidity and mortality (Pasqua, 2013; Shannon, 2010; Nici, 2009). Palliative care improves the quantity and quality of life in individuals with lung cancer (Davis, 2012; see chapter 19, End of Life Issues/Palliative Care).
Pulmonary Fibrosis

The clinical syndrome of combined pulmonary fibrosis and emphysema (CPFE) has recently been defined by the presence of breathlessness, upper lobe emphysema, lower lobe fibrosis, and deranged pulmonary gas exchange (Jankowich, 2012). Nearly all patients with this syndrome have been smokers and 90% are male (Jankowich,
Pulmonary Fibrosis

Patients typically present with breathlessness and pulmonary physiologic testing reveals profoundly reduced DLCO but relatively preserved lung volumes due to pseudonormalization. This effect is due to the opposite effects of the fibrosis which reduces lung volumes and emphysema which causes hyperinflation; these two opposing forces result in relatively normal lung volumes whereas both adversely affect DLCO, causing it to be disproportionately reduced. (Figure 10.2 and 10.3). The reduction in DLCO is associated with significant hypoxemia and requirement for supplemental oxygen (Cottin, 2005). The chest radiograph often shows basilar reticulo-linear opacifications with reduced upper zone lung markings (Figure 10.4 and

<table>
<thead>
<tr>
<th>Diagnosis: Chronic Obstructive Pulmonary Disease</th>
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<tbody>
<tr>
<td>Dyspnea: After any exertion</td>
</tr>
<tr>
<td>Tobacco</td>
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<td>Medications:</td>
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</table>

Post Test Comments:

PLEASE REFER TO THE COMPUTERIZED RECORD FOR THE ORDER AND INTERPRETATION OF THESE RESULTS. ATTENTION: PFT NOT VERIFIED UNTIL REVIEWED BY ATTENDING. Good patient effort & cooperation. SaO2 on 2 LPM=91%. 2 puffs of Proventil given via aerochamber with 1 min between puffs, 10 minutes elapsed before post tests. Patient given outpatient medication list. Patient reviewed list and reported no discrepancies. No recent Hg available. Patient difficulty exhaling maximally during all tests due to coughing. He used 2 LPM during DLCO maneuver (pt only able to complete one test). Extra time given, patient was short of breath during testing.

--- SPIROMETRY ---

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>FVC (L)</td>
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<td>Pred: 4.56</td>
</tr>
<tr>
<td>FEV1 (L)</td>
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</tr>
<tr>
<td>PEV/FVC (%)</td>
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<td>Pred: 75</td>
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<tr>
<td>PEF Max (L/sec)</td>
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<tr>
<td>PEF 25-75% (L/sec)</td>
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--- LUNG VOLUMES ---

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<tr>
<td>TLC (L)</td>
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</tr>
<tr>
<td>FVC (L)</td>
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</tr>
<tr>
<td>RV (L)</td>
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<td>Pred: 1.13</td>
</tr>
<tr>
<td>IC (L)</td>
<td>Actual: 2.05</td>
<td>Pred: 3.40</td>
</tr>
<tr>
<td>RV/IC (L)</td>
<td>Actual: 3.10</td>
<td>Pred: 2.49</td>
</tr>
<tr>
<td>RV/TLc (%)</td>
<td>Actual: 47</td>
<td>Pred: 39</td>
</tr>
<tr>
<td>Raw (cmH2O/L/sec)</td>
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<td>Pred: 1.45</td>
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<tr>
<td>Gmax (L/min/cmH2O)</td>
<td>Actual: 0.75</td>
<td>Pred: 1.03</td>
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--- DIFFUSION ---

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</thead>
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<td>Pred: 21.91</td>
</tr>
<tr>
<td>DLCO (ml/min/mmHg)</td>
<td>Actual: 8.53</td>
<td>Pred: 21.91</td>
</tr>
<tr>
<td>VA (L)</td>
<td>Actual: 4.70</td>
<td>Pred: 6.72</td>
</tr>
<tr>
<td>DL/VA (ml/min/mmHg/L)</td>
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<td>Pred: 4.15</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>Actual: 3.12</td>
<td>Pred:</td>
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Chest CT scans demonstrate emphysematous changes in the upper lung zones and reticular opacifications with honeycombing in the lung bases. (Figure 10.6) The median survival is only 2.1–8.8 years and is adversely affected by the development of pulmonary hypertension and lung cancer which occur frequently in association with CPFE.

Treatment of CPFE depends upon early recognition and smoking cessation, institution of supplemental oxygen to prevent desaturation, and management of COPD. It is not yet known whether the recently discovered effective treatments for idiopathic pulmonary fibrosis, pirfenidone or nintedanib, are beneficial in patients with CPFE. It is also not known whether PH treatment modulates the disease course. Lung cancer screening has not been assessed in patients with CPFE but the increased incidence of lung cancer would suggest potential benefit to earlier detection if the patients are candidates for surgical resection.
Although polycythemia associated with hypoxemia is often considered the principle hematologic manifestation of COPD, anemia occurs in 7.5–32.7% of patients with COPD (Yohannes, 2011; Cote, 2007; Chambellan, 2005; Shorr, 2008; Nowinski, 2011; Portillo, 2013). Only 6% of 683 patients with COPD had polycythemia whereas 17% had anemia (Cote, 2007). COPD–related anemia is characterized by a normal to low MCV, low serum iron, and normal to increased ferritin and is associated with higher systemic inflammation (including IL6 and CRP), greater healthcare costs, and mortality (Kollert, 2013). The anemia of COPD is believed to be due to chronic inflammation (anemia of chronic disease). Inflammatory cytokines such as TNF α and IL6 suppress hepcidin synthesis and inhibit erythropoietin which decreases iron availability and decreases erythropoiesis.

Figure 10.5: Lateral chest radiograph from a patient with combined pulmonary fibrosis and emphysema.
Anemia in patients with COPD is associated with higher levels of dyspnea and diminished 6 minute walk distances (Cote, 2007) and anemic individuals with COPD have reduced exercise capability during cardiopulmonary exercise testing with greater breathlessness (Bouton, 2011). Patients with COPD and anemia have worse quality of life measured by the physical functioning and physical component scores on the Short Form-36 survey compared with those with normal hemoglobin levels (Krishnan, 2006). Anemia is associated with increased healthcare utilization, prolonged
length of hospital stay, more frequent readmissions, greater healthcare costs, and mortality among individuals with COPD (Chambellan, 2005; Shorr, 2008; Nowinski, 2011; Halpern, 2006; Barba, 2012; Martinez-Rivera, 2012; Martinez-Rivera, 2012; Celli, 2004). The one year mortality after hospitalization for a COPD exacerbation was approximately 40% in anemic individuals but only 10% in those with normal hemato­crits (Martinez-Rivera, 2012).

It is not known whether treatment of anemia associated with COPD improves survival, alters respiratory symptoms, reduces healthcare utilization, or COPD related health care costs. Red blood cell transfusions may assist in ventilator liberation and reduce minute ventilation and work of breathing in critically ill patients with COPD who require mechanical ventilator support (Schonhofer, 1998A, 1998B).

The number of circulating bone marrow-derived progenitor cells is reduced in patients with COPD (Huertas 2011, 2010; Palange, 2006; Fadini, 2006)

10.8 Musculoskeletal

The prevalence of osteoporosis is greatly increased in individuals with COPD and ranges from 24–69% depending upon the population studied and the severity of AFL (Graat-Verbom, 2009). Vertebral fractures occur in 24%-63% of patients with COPD and predominantly involve T7, T8, and T12 (Jorgensen, 2007; Nuti, 2009; Papianniou, 2003; McEvoy 1998). Approximately 10% of patients admitted with COPD exacerbations have chest radiographs documenting vertebral compression fractures (Majumdar, 2010). These compression fractures may decrease patients’ heights affecting the normative equations for predictive values used in the interpretation of pulmonary function testing. Therefore, it may be beneficial to consider using arm span in determining the predicted normal values in patients with COPD who have severe vertebral fracture associated kyphosis. Further, the vertebral fractures may lead to a reduction in lung volumes. Each vertebral fracture is associated with a 9% reduction in the FVC (Leech, 1990).

Osteoporosis is more prevalent in patients with COPD who have emphysema and an increase in the RV to TLC ratio, a lower BMI, are older, have used systemic steroids or chronic supplemental oxygen, and have worse AFL (Graat-Verbroom, 2012; Ogura-Tomomatsu, 2012). Systemic inflammation measured by CRP, TNFα and IL 6 is greater in patients with COPD with osteopenia or osteoporosis than in those individuals with normal bone density (Liang, 2011).

Of 12,646 Veterans undergoing hip fracture surgery in the VHA from 1998 to 2005, 5,944 (47%) had COPD and a diagnosis of osteoporosis was known before the hip fracture in only 3% of cases (Regan, 2013). Using the FRAX® tool to estimate the risk of hip fracture in Spanish patients admitted with an acute exacerbation of COPD, 1.8% (95%CI: 0.9–3.6) had a 10 year probability of > 20% for a major osteoporotic fracture and 49.7% (95% CI: 44.8–54.7) had a probability of hip fracture >3% (Diez-Mangiano,
Thus, nearly half of individuals with hip fractures have COPD and the presence of COPD portends a very high likelihood of future hip fracture.

The 3 year fracture rate HR ranged from 5.1–6.3 across the various treatment and placebo groups in the TORCH trial (Ferguson, 2009). Hip fractures occurred most commonly, followed by wrist, spine, and rib fractures.

10.8.1 Risk Factors for Fractures in Individuals with COPD

Osteoporosis and falls are major risk factors for fractures and occur commonly in individuals with COPD. In an analysis of 14,828 subjects participating in the National Health and Nutrition Examination Survey (NHANES) from 1999–2008, individuals with physician-diagnosed COPD were more likely than those without physician-diagnosed COPD to have osteoporosis (16.9% vs 8.5%) and more likely to report mobility difficulty (55.6% vs 32.5%) and dizziness/balance problems (41.1% vs. 23.8%) (Schnell, 2012)

10.8.2 Osteoporosis

In individuals with COPD, the prevalence of osteoporosis and osteopenia range from 9–69% and 27–67%, respectively (Graat-Verboom, 2009; Lehouck, 2011; Graat-Verboom, 2011; Jorgensen, 2007; Rittayamai, 2012). In a longitudinal cohort study of 102 patients with COPD, 16 of 48 (33%) patients with normal initial bone density developed osteoporosis over 3 years (Graat-Verboom, 2012). In the TORCH trial, 18% of men and 30% of women had osteoporosis and 42% of men and 41% of women had osteopenia at baseline based on bone mineral density measurements (Ferguson, 2009).

Evaluation of bone mineral density in patients with COPD should include a comprehensive history and physical examination to identify risk factors associated with reduced bone mineral density, fractures, and bone loss, determination of vitamin D levels, DEXA, and spine radiographs, especially in individuals with back pain, height loss, or kyphosis (Mazokopakis, 2011). Treatment of osteoporosis in individuals with COPD includes pharmacologic and nonpharmacologic interventions (Table 10.1).

10.8.3 Falls

Despite the presence of multiple predisposing factors to falls, the prevalence and incidence of falls in individuals with COPD has not been studied extensively. In a study comparing 36 patients with COPD with 20 normal individuals, hypoxemia, dyspnea, and fatigue were associated with balance impairment and falls (Ozalevli, 2011). In a retrospective study, 46% of 39 participants with COPD (mean FEV1% predicted
42%) reported at least one fall in the preceding year. Those with self-reported falls scored lower on the Activity-Specific Balance Confidence (ABC) Scale (66 v 82) and the Berg Balance Scale (BBS) (45 v 49), and had prolonged times on the Time Up and Go Test (TUG) 17 v 14 s. Falls correlated with the use of supplemental oxygen and dyspnea severity (Beauchamp, 2009). Another retrospective study found that 25% of 80 patients with COPD (mean FEV\textsubscript{1} % predicted 47.5%) reported a fall in the prior year and 29% expressed a fear of falling (Hellstroem, 2009). In a prospective study of 101 patients with COPD (mean FEV\textsubscript{1} % predicted 46%) for 6 months, 31.7% reported at least one fall and the fall incidence rate was 0.1 (95% CI: 0.06–0.14) falls per person/month. Risk factors for falls included age, sex, oxygen requirement, history of prior falls, co-morbidities, number of medications (Roig, 2011A).

Factors contributing to the increased risk of falling in patients with COPD include alterations in proprioception (Janssens, 2013), impaired postural and balance control mechanisms (Roig, 2011B; Beaucham, 2009; Butcher, 2004; Eisner, 2008; Smith, 2010), slower reaction times, reduced physical activity levels, and skeletal muscle weakness (Beauchamp, 2012).

### 10.8.4 Muscle Weakness

Skeletal muscle dysfunction in patients with COPD is characterized by muscle atrophy (decreased mass and cross-sectional area), deranged distribution of fiber types (fewer oxidative fibers and more glycolytic fibers), altered metabolic capacity (diminished mitochondrial enzyme activities and expression), and reduced vascular supply (loss of capillary density) that cause diminished muscle strength and endurance (Kim, 2008; Gea, 2013). Factors that contribute to skeletal muscle dysfunction include disuse and inactivity, systemic inflammation, malnutrition, corticosteroid use, hypoxemia, senescence, and myocyte biochemical derangements including reactive oxygen and nitrogen species production, and muscle fiber degradation due to increased calpain and caspase activities (Kim, 2008). Quadriceps muscle strength is

<table>
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<tr>
<th>Management of Osteoporosis</th>
<th>Associated with COPD</th>
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<tr>
<td>Calcium and vitamin D</td>
<td>Balanced nutrition</td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td>Smoking cessation</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>Exercise, including pulmonary rehabilitation</td>
</tr>
<tr>
<td>Strontium ranelate</td>
<td>Fall prevention</td>
</tr>
<tr>
<td>Denosumab</td>
<td>Lung volume reduction surgery (Mineo 2005)</td>
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</tbody>
</table>
20–30% less in individuals with moderate to severe COPD compared with those who do not have COPD (Gosselink, 1996; Bernard, 1998; Franssen, 2005).

10.9 Diabetes

Approximately 12.6–14.5% of individuals with COPD have diabetes mellitus (DM) (Mannino, 2008; Laghi, 2009). Patients with COPD have an odds ratio of developing diabetes of 2.04 [1.97–2.12] compared with those who do not have a physician diagnosis of COPD (Feary, 2010). The relative risk of diabetes is 1.8 [1.1–2.8] in patients with COPD compared with those with asthma (Rana, 2004). The presence of both DM and COPD increases the risk of death and the length of hospitalizations for patients with AECOPD and diabetes is 10.3% longer than those who do not have DM (Burt, 2013; Parrapil, 2010; Emerging Risk Factors Collaborative, 2011). In one study, the length of stay increased by 10% for each mmol/L increase in mean glucose level (Burt, 2013).

Treatment with prednisone is associated with afternoon and evening hyperglycemia rather than elevated morning glucose levels (Burt, 2011). Therefore, it may be beneficial to monitor glucose levels later in the day and adjust insulin type and dosing for individuals with COPD and DM who require insulin and are being treated with long term corticosteroids.

Individuals with COPD and metabolic syndrome have more frequent and longer exacerbations than those who do not have metabolic syndrome (Kupeli, 2010).

10.10 Conclusion

Over the past decade, COPD has been recognized as a systemic process that extends beyond the lungs to involve nearly all other organs and systems. This widespread involvement is believed to be mediated through systemic inflammation. Respiratory failure is the major cause of mortality in individuals with more severe respiratory impairment whereas cancer and cardiovascular processes predominant in those individuals with more mild airflow limitation. Death due to respiratory causes has been decreasing with improvements in COPD management but mortality due to nonrespiratory causes is increasing. The systemic manifestations of COPD are increasingly being recognized as contributing to the mortality and morbidity caused by COPD. The increase in nonrespiratory related mortality and morbidity suggests that earlier identification and management of nonpulmonary processes associated with COPD may be warranted to improve the longevity and health of individuals with COPD.
### 10.11 Summary Points

1. Comorbidities associated with COPD contribute significantly to COPD mortality and morbidity.
2. In individuals with similar smoking histories, the presence of airflow limitation increases the risk of lung cancer by approximately 3–4 fold.
3. Ischemic heart disease and heart failure contribute significantly to COPD morbidity especially in those with less severe disease (more mild to moderate AFL).
4. Individuals with COPD can be treated safely with β blockers and, with concurrent myocardial ischemia, have lower mortality than those who do not receive β blockers; in contrast, β agonists are associated with increased morbidity and mortality especially in patients with COPD and heart failure.
5. Fractures occur more often in individuals with COPD due to increased prevalence of osteoporosis/penia, muscle weakness, and gait and balance instability.
6. Increased awareness, detection, and treatment of nonpulmonary manifestations of COPD will be critical in improving quality of life and wellbeing of individuals with COPD.

### References


References


Ralph J. Panos, MD

11 Sleep and COPD: The Overlap Syndrome

Key Points
1. Sleep disturbances occur in 34–78% of patients with COPD due to nocturnal respiratory symptoms, intrinsic sleep disordered breathing, or a combination of both processes.
2. The overlap syndrome is the concurrence of COPD and obstructive sleep apnea (OSA).
3. Although the prevalence of OSA among those with COPD was initially thought to be increased, more recent studies suggest that the prevalence of the overlap syndrome is about 1% of the general population which is the predicted prevalence if COPD and OSA are independent processes.
4. The recognition and identification of sleep disordered breathing among patients with COPD requires a strong index of suspicion and a sleep-directed history and physical examination.
5. Overlap syndrome is characterized by more profound nocturnal hypoxemia and deranged sleep architecture than either COPD or OSA alone.
6. The physiologic derangements of COPD accentuate normal sleep-related respiratory changes to cause hypoventilation and ventilation-perfusion mismatching during sleep increasing PaCO$_2$ and decreasing PaO$_2$.
7. Management of the overlap syndrome includes optimal treatment of COPD and use of noninvasive positive pressure ventilation for the OSA.

11.1 Introduction

Sleep quality is worse in individuals with COPD compared with those without COPD (Fleetham, 1982; Calverley, 1982; Brezinova, 1982). Between 34 and 78% of individuals with COPD report difficulty initiating or maintaining sleep, nocturnal awakenings, or nonrestorative sleep (Agusti, 2011; Tashkin, 2008; Price, 2013, Weizenblum 2004; Marrone, 2006; Klink, 1994; Rennard, 2002). Sleep efficiency is only 50–70% in patients with COPD and the proportion of sleep time is increased in light sleep and decreased in REM sleep, shifts between sleep stages occur more frequently, and micro-arousals disrupt sleep (McNicholas, 2013). At least half of all patients with COPD experience nocturnal respiratory symptoms (Miravitlles, 2014). Some studies suggest that this proportion increases as lung function worsens whereas other investigations show no relationship between nocturnal respiratory symptoms and COPD severity (Kessler, 2011; Lange, 2014; Miravitlles, 2014).

Nocturnal symptoms are associated with worse sleep quality, greater daytime breathlessness, more frequent COPD exacerbations, and greater number of respira-
tory medications (Price, 2011; Miravitlles, 2014). In addition, patients with nocturnal respiratory symptoms have greater dyspnea, anxiety, and depression and worse health status (Miravitlles, 2014). Nocturnal breathlessness is associated with daytime respiratory symptoms including dyspnea, phlegm production, and wheezing (Lange, 2014; Miravitlles, 2014; Kessler 2011).

Approximately one third of patients with OSA have chronic cough (Chan, 2010). Those with cough have similar sleep and respiratory symptoms but are more likely to be female and have more rhinitis and nocturnal gastrointestinal reflux symptoms than those without cough. In a group of 75 patients with chronic cough, 44% had OSA and 93% of them had improvement in their cough with optimized CPAP treatment (Sundar, 2010). Thus, OSA may contribute to chronic cough in patients with COPD and the cough may be improved with CPAP.

Physicians greatly underestimate the prevalence of nocturnal symptoms and their effects in patients with COPD (Price, 2011). Conversely, only 11.8% of patients with COPD discuss sleep concerns with their provider (Ohayon, 2014). The Nighttime Symptoms of COPD Instrument is a recently developed and validated patient-reported outcome instrument to document nocturnal symptoms in patients with COPD which may help in the recognition of night-time manifestations of COPD (Hareendran, 2013).

In addition to OSA, other sleep disorders that occur in individuals with COPD can include insomnia, periodic limb movement syndrome, and psychiatric sleep disorders (Ohayon, 2014; Valipour, 2012). Approximately half of all patients with COPD have insomnia symptoms, which is twice the prevalence as in those who do not have COPD (Ohayon, 2014). Concurrent depression or anxiety increases the prevalence of insomnia to 84.4% and 59.7%, respectively (Ohayon, 2014). Insomnia symptoms appear to correlate positively with COPD severity measured by the BODE index, current smoking, and greater sadness/anxiety and negatively with supplemental oxygen use (Hynninen, 2013; Budhiraha, 2012). Periodic limb movement and psychiatric sleep disorder scale scores derived from the Sleep Disorders Questionnaire are greater in patients with mild to moderate COPD compared with those who do not have obstructive lung disease (Valipour, 2012).

### 11.2 Smoking, Sleep, and COPD

Inhalation of tobacco smoke is the major cause of COPD (See Chapter 9, Natural History, Phenotypes, and Gender Differences in COPD and Chapter 6, Pathogenesis of COPD). Many patients with COPD continue to smoke and tobacco smoke inhalation is associated with sleep disturbances including reduced sleep efficiency, increased sleep latency, nonrestorative sleep, and alterations in sleep stages with less REM sleep and more time in lighter sleep (Lan, 2012; Wetter, 1994A; Wetter, 1994B; Zhang, 2006; Zhang, 2008; Jaehne, 2009). Some smokers may experience nocturnal partial nicotine withdrawal which can disrupt sleep by inducing frequent and prolonged awakenings.
(Philips, 1995). Former smokers who have completely quit smoking have a similar sleep architecture to never smokers, so the effects of smoking on sleep appear to reverse once smoking cessation is achieved (Zhang, 2006; Soldatos, 1980).

Smoking has also been associated with the development of OSA and some researchers have proposed that OSA may contribute to nicotine addiction (Lin, 2012). In a study of 811 individuals undergoing polysomnography, current smokers were more likely to snore, odds ratio (OR) 2.26 (95% confidence interval (CI), 1.46, 3.49), and to have sleep disordered breathing, OR 1.64 (95% CI, 0.94–2.86), and this risk was greatest among those who smoked more than 2 packs per day, OR 8.39 (95% CI, 1.68–41.94) (Wetter, 1994A). Smoking prevalence is higher in individuals with OSA than in those who do not have sleep disordered breathing, 35% and 18%, respectively (Kashyap, 2001). The period of smoking cessation is associated with sleep alterations including more arousals and worse sleep quality that correlate with poorer smoking cessation rates (Jaehne, 2009). Further, weight gain often accompanies smoking cessation and can either worsen existing OSA or increase the risk of its development (Williamson, 1991; Peppard, 2000). Nicotine may have beneficial effects in individuals with OSA. It increases the tone of posterior pharyngeal dilator muscles helping to maintain upper airway patency and, thereby, reduces resistance to airflow (Haxhiu, 1984). Nicotine also stimulates the phrenic nerve increasing diaphragmatic activity (Haxhiu, 1984). Because of these potential beneficial effects, nicotine has been evaluated for the treatment of OSA. A small study showed that enteral nicotine reduced the number of apneas during the initial hours of sleep (Gothe, 1985) but a subsequent study showed that transdermal nicotine had no effect on the number of apneas and hypopneas or snoring intensity in patients with habitual snoring (Davila, 1994). Nicotine delivered locally to the posterior pharynx via a tooth patch increases salivary nicotine levels but has no effect on the number of apneas or hypopneas in patients with OSA (Zevin, 2003).

11.3 Prevalence of Overlap Syndrome

In 1985, David Flenley coined the term overlap syndrome to refer to the coexistence of OSA and any chronic respiratory disorder and, over the past three decades, overlap syndrome has been most commonly used to denote the concurrence of COPD and OSA (Flenley, 1985; Weitzenblum, 2008). Earlier studies suggested that the prevalence of OSA was increased among individuals with COPD. However, these studies sampled populations from sleep or respiratory clinics and their conclusions may be affected by selection bias. The prevalence of the overlap syndrome among men is estimated to be approximately 1% (Chaouat, 1995; Ioachimescu, 2013; Sanders, 2003; Bednarek, 2005; McNicholas, 2009; Owens 2010). If one estimates a prevalence of 10% for both COPD and OSA, the expected prevalence of the overlap syndrome is 1%. However, since both COPD and OSA are under-recognized and under-diagnosed,
the actual prevalence of the overlap syndrome is most likely greater than reported or estimated.

The largest epidemiologic study of the overlap syndrome analyzed the 5,954 participants in the Sleep Health Heart Study who underwent unattended home polysomnography testing and spirometry (Sanders, 2003). This study was designed to address the relationship between sleep disordered breathing and hypertension and cardiovascular disease in adults and oversampled individuals younger than 65 years old who snored. The proportion of participants with OSA with or without airflow limitation was similar, 22.32% versus 28.86%, or 13.97% versus 18.63%, using apnea-hypopnea index (AHI) thresholds of either >10 or >15 events/hour to define OSA, respectively (Sanders, 2003). The AHI was positively correlated with the FEV₁/FVC ratio, suggesting that among individuals with mild airflow limitation, more severe obstruction was associated with a lower AHI. Participants with both airflow limitation and OSA had greater sleep disturbances and greater nocturnal desaturations than those with either disorder alone. The OR for nocturnal desaturation (defined as SpO₂ <90% for more than 5% of total sleep time) was 3.36 (95% CI, 1.98, 5.70) in those with an FEV₁/FVC ratio less than 60% and as the FEV₁/FVC ratio declined the proportion of participants with nocturnal desaturation increased (Sanders, 2003). Participants with overlap syndrome had higher Epworth Sleepiness Scale scores (a measure of sleepiness), and greater proportions of total sleep time in stage 2 and less time in REM and stage 3/4 sleep than those with either disorder alone (Sanders, 2003). Thus, the Sleep Health Heart Study showed that the prevalence of OSA is not increased among individuals with mild COPD but those with the overlap syndrome do have more deranged sleep architecture and greater nocturnal oxygen desaturation than those with either disorder alone.

The results of the SHHS were corroborated by the Monica II study that showed that the prevalence of airflow limitation in participants with OSA was the same as in the general population, approximately 10–11% (Bednarek, 2005). Those with the overlap syndrome had a lower mean SpO₂ and spent more time with a SpO₂ <90%.

11.4 Predictors of Overlap Syndrome

Among individuals with COPD, the risk of sleep disordered breathing increases with body mass index (BMI), age, smoking status, presence of peripheral edema, and use of systemic steroids (Chaouat, 2005; McNicholas, 2013). A small study of 177 subjects with COPD, 33 of whom had OSA, suggested that BMI and smoking history measured in pack years were associated with the AHI (Steveling, 2014). A recent study of patients with overlap syndrome did not find that they were more obese or had more excessive daytime sleepiness than those who did not have OSA and suggested that a high index of suspicion is needed to recognize and diagnose overlap syndrome (Venkateswaran, 2014).
The GOLD Guidelines recommend screening patients with COPD for OSA if they are experiencing sleep related symptoms or excessive nocturnal awakenings (GOLD). Because of the high association of pulmonary hypertension with the overlap syndrome, screening sleep studies may be indicated in individuals with COPD and elevated pulmonary artery pressures (See Chapter 12, COPD and Pulmonary Vasculature) (Celli, 2004). A small retrospective study found an association between the severity of airflow and the presence of OSA and suggested that sleep studies should be considered in patients with severe COPD (Lopez-Acevedo, 2009). However, another study did not find an association between OSA and severity of airflow limitation among patients with COPD (Sharma, 2011). In patients with the overlap syndrome, lung hyperinflation measured by the inspiratory capacity divided by the total lung capacity (IC/TLC) correlates with worse sleep efficiency independent of the AHI or severity of hypoxemia; therefore, the presence of hyperinflation might be another screening pulmonary physiologic variable to consider in determining which patients to evaluate for overlap syndrome (Kwon, 2009).

11.5 Screening and Diagnosis

The recognition and diagnosis of COPD is discussed in Chapter 3, COPD Recognition and Diagnosis. A high level of vigilance and attentiveness are required for the recognition and diagnosis of OSA in patients with COPD.

A comprehensive sleep history is an important first step in the evaluation of patients with COPD and sleep related symptoms. The discrimination of sleep disordered breathing due to intrinsic sleep disorders from disrupted sleep due to nocturnal respiratory symptoms can be difficult. The sleep history and examination may increase the suspicion of obstructive sleep apnea or other sleep disturbance, but polysomnography is required to establish the diagnosis and initiate treatment.

In general, patients who are obese, have highly associated comorbidities such as congestive heart failure, atrial fibrillation, hypertension that is difficult to control, pulmonary hypertension, and who work in potentially high risk occupations (pilot, school bus driver) should be evaluated further (Epstein, 2009). Another key historical feature is previous motor vehicle accidents especially if they are related to sleepiness. Key elements of the sleep history include sleep initiation including insomnia, total sleep time, quality of sleep (restorative versus nonrestorative), presence or absence of recalled dreams, snoring, observed apneas or episodes of choking, gasping, or sputtering, excessive daytime sleepiness, nocturnal awakenings including nocturia, morning headache, excessive daytime sleepiness, reduced memory, and emotional lability (Epstein, 2009). A review of the accuracy of the clinical history in the diagnosis of OSA showed that a history of choking or gasping at night was the most predictive historical finding, summary likelihood ratio (LR), 3.3; (95% CI, 2.1–4.6) when an AHI ≥10/h was used to diagnose OSA (Myers, 2013). Although patients with OSA fre-
sequently reported snoring, it was not useful in discriminating OSA (summary LR, 1.1; 95% CI, 1.0–1.1) (Myers, 2013). Thus, in individuals with COPD, these discriminating characteristics may not be as reliable and the clinician should consider a careful sleep history while maintaining a high index of suspicion for sleep disturbances. Finally, it may be difficult to differentiate sleep dysfunction related to respiratory symptoms due to COPD such as cough and sleep symptoms related to OSA.

Several validated surveys are available to assist clinicians in the identification of individuals at risk for sleep disordered breathing. The Epworth sleepiness scale is a measure of sleep propensity and correlates with sleep latency, the apnea hypopnea index, and minimal nocturnal SpO₂ in individuals with OSA (Johns, 1991). The Berlin questionnaire is a screening survey for OSA in the general population that has a sensitivity and specificity of 86% and 77%, respectively, in primary care patients (Netzner, 1999). The Nighttime Symptoms of COPD Instrument assists in the identification of nocturnal respiratory symptoms (Hareendran, 2013). The use of these instruments in the overlap syndrome is less well studied.

Elements of the physical examination may also suggest the presence of OSA. Hypertension, especially when it is refractory to treatment, and elevated body mass index are abnormal vital signs that may be associated with OSA. An increased neck circumference, reduced posterior pharyngeal diameter, enlarged tonsils, and retroglossia may also increase the risk of OSA.

There are no elements of the history or physical examination that can conclusively diagnose OSA and further evaluation with a form of sleep diagnostic testing, formal full polysomnographic study in a sleep laboratory or home study, is usually indicated. Overnight pulse oximetry has limited utility in the diagnosis of OSA in patients with COPD and is not reliable for the diagnosis of the overlap syndrome due to the indiscriminant frequency, pattern, and severity of oxygen desaturation events in both disorders (Scott, 2014).

### 11.5.1 Normal Sleep Physiology

Physiologic regulation of respiration during wakefulness is an integrally connected tripartite system of sensors, central control, and effectors. Aortic and carotid body sensors monitor changes in oxygen and carbon dioxide, vagal afferent neurons sense lung parenchymal alterations, and other systems respond to external stimuli and volitional control (Newton, 2014). Within the medullary ventilator center, neurons generate an automated respiratory rhythm that is modulated by these sensory and volitional inputs. The signals from the respiratory center stimulate the diaphragm and other respiratory muscles to generate inspiratory and expiratory airflow and maintain upper airway muscle tone and patency modulating both respiratory frequency and tidal volume. This system is highly regulated to maintain usual PaO₂ and PaCO₂ levels within narrow ranges.
Respiratory physiology is markedly altered during sleep and the ventilatory changes vary during different stages of sleep. With sleep onset, external stimuli and volitional signals are no longer processed or produced and internal biochemical and biomechanical sensory inputs predominant. The usual change from primarily upright to horizontal posture alters thoracic musculoskeletal and diaphragmatic mechanics and may also affect posterior pharyngeal architecture by reducing the airway lumen. During sleep, respiratory center responses to biochemical stimuli, $\text{PaO}_2$ and $\text{PaCO}_2$, are blunted. Combined with a lower metabolic rate, the diminished chemosensitivity to oxygen and carbon dioxide levels causes a reduction in minute ventilation mainly through a decrease in tidal volume. Consequently, $\text{PaCO}_2$ rises and $\text{PaO}_2$ may decline slightly. During REM sleep, skeletal muscle atonia occurs and the diaphragm is the only functioning respiratory muscle which reduces tidal volume and minute ventilation and further accentuates hypoxemic and hypercarbic changes.

### 11.5.2 Sleep Physiology and OSA

OSA is diagnosed by the presence of either cessation (apnea) or reduction (hypopnea) of airflow caused by recurrent upper airway occlusion or blockage during sleep despite maintained central respiratory drive. These events are measured by the apnea-hypopnea index (AHI), the number of apneas and hypopneas per hour, and OSA is usually defined as an AHI greater than 5 events per hour. Central sleep apnea is caused by the absence of central respiratory drive stimuli. Initiation and maintenance of airflow during sleep requires central signaling, activation of respiratory muscles including not only the diaphragm and accessory muscles, but also those controlling the posterior pharyngeal lumen to maintain upper airway patency and counteract the inward negative pressure of inspiration. If the airway aperture is not maintained, airflow is reduced (hypopnea) or stopped (apnea). Depending upon the duration and severity of reduced airflow, $\text{PaCO}_2$ levels may rise and $\text{PaO}_2$ levels decrease. Apneic or hypopneic events are usually terminated by an arousal followed by augmented minute ventilation to normalize oxygen and carbon dioxide levels. Reduced biochemical sensitivity may derange normal feedback loops causing over or under compensation and wide variation in respiratory patterns. These arousals lead to sleep fragmentation and reduced REM sleep time. Factors that may contribute to the development of OSA include individual anthropomorphic features, upper airway architecture which is determined by anatomic, mechanical, and neuromuscular processes, medications including alcohol, and respiratory center function (Deegan, 1995).
11.5.3 Sleep Physiology and COPD

COPD-related respiratory derangements may adversely affect normal sleep physiology. Supine positioning during sleep may reduce the posterior pharyngeal aperture increasing airway resistance. Resistance to airflow is greatest in the posterior pharynx in the region circumscribed by the base of the tongue and the soft palate. The airway in this zone is flexible and potentially collapsible. The base of the tongue may move posteriorly and approach the posterior pharyngeal wall reducing the anterior-posterior aperture and the lateral walls may also encroach upon the lumen due to excessive soft tissue, mucosal edema and inflammation, negative intraluminal pressure during inspiration, and relaxed pharyngeal dilator muscle tone (Mieczkowski, 2014). This increase in upper airway resistance necessitates generation of a greater inspiratory force by the respiratory muscles which may be handicapped due to intrinsic muscle weakness related to COPD and mechanical disadvantages.

Intrinsic muscle dysfunction associated with COPD may affect the upper airway musculature as well as the diaphragm and accessory muscles of respiration diminishing their function. In individuals with hyperinflation and air trapping, the diaphragm may be mechanically disadvantaged due to elongation and distension of diaphragmatic muscle fibers. Hyperinflation is associated with worse sleep efficiency in patients with overlap syndrome (Kwon, 2009). Additionally, the pressure of abdominal contents in the supine positioning further disadvantages the diaphragm by increasing its load due to the additional caudad force required for movement during inspiration. Individuals with COPD and hyperinflation may be more reliant upon accessory muscles of respiration to maintain minute ventilation; the hypotonia of REM sleep may further reduce minute ventilation by eliminating the contribution of accessory muscles to ventilation. These physiologic changes may cause more profound hypoxemia, up to 40% declines in oxygen saturation during REM sleep and 20% reductions during non-REM sleep, in patients with severe COPD (Becker, 1999).

11.5.4 Sleep Physiology and Overlap Syndrome

COPD-related respiratory derangements may augment and accentuate many of the physiologic consequences of OSA. Patients with the overlap syndrome generally have more profound sleep-related hypoxemia and hypercarbia than individuals with either disorder alone (McNicholas, 2013). Factors that may contribute to hypoxemia severity in the overlap syndrome include lower baseline oxygen level, ventilation/perfusion mismatching, and blunted oxygen sensing. Worsened ventilation perfusion mismatching due to reductions in functional residual capacity, supine posture, intrinsic parenchymal lung disease, retained secretions occluding or blocking airways, may contribute to nocturnal desaturations in individuals with COPD (McNicholas, 2013).
Although isocapnic hypoxemia is not a usual stimulus for arousal during sleep and desaturations to 70% may not trigger awakenings, individuals with COPD may have resting low normal oxygenation levels that place them on the shoulder of the oxygen-hemoglobin desaturation curve. Thus, even slight declines in oxygenation may precipitate severe desaturation. An increase of approximately 15 mmHg in end tidal carbon dioxide level is the threshold for usual hypercapnic-induced arousals but patients with COPD and hypercarbia may have severely blunted responses to further increases in carbon dioxide levels (Ayas, 2000).

Both COPD and OSA are characterized by systemic inflammation. The pathophysiology and consequences of inflammation in COPD are discussed in Chapter 6, Pathogenesis of COPD and Chapter 10, COPD is a Multi-Organ Disorder: Systemic Manifestations. OSA is categorized by enhanced production of inflammatory cytokines, sympathetic nervous system activation, and abnormal vascular and coagulant function. Recurrent hypoxic stress and sleep disruption are believed to be primary etiologic factors. The relationship between etiologic processes underlying systemic inflammation in the overlap syndrome and its component disorders, COPD and OSA, is an active area of research.

As discussed below in Comorbidities, the prevalence of comorbidities including COPD exacerbations and cardiovascular events related to inflammation and excessive mortality in the overlap syndrome appears to be greater than can be accounted for by either OSA or COPD alone suggesting a synergistic interaction.

### 11.6 Ventilation and Ventilation Perfusion Matching

During sleep, the cough reflex is diminished and the normal clearance of respiratory secretions (the production of which is increased in chronic bronchitis and bronchiectasis) is reduced (Power, 1984). These secretions may accumulate within the airways causing partial or total occlusion increasing airway resistance and altering ventilation patterns. These perturbations may disrupt ventilation-perfusion matching precipitating lower oxygenation and desaturation.

### 11.7 Polysomnography

Polysomnography (PSG) is the usual diagnostic study to evaluate sleep disordered breathing. PSG tests are multimodality studies that usually include electroencephalographic (EEG), electrooculographic (EOG), electrocardiographic (ECG), and electromyographic (EMG) measurements as well as monitoring pulse oximetry, thoracic and abdominal respiratory efforts, and audiovisual recording. Based upon EEG and EOG tracings, sleep is categorized into wakefulness, N1, N2, N3, and REM sleep (Silber, 2007). Most individuals progress through the nonREM stages to REM several times
during the night with more time in deep, N3 sleep during the early cycles and an increasing proportion of time in REM during the later cycles prior to awakening. Normally deep N3 sleep and REM sleep each account for approximately one quarter of sleep time and the remaining half of sleep time is transitional N1 and N2 sleep.

### 11.7.1 Consequences of Overlap Syndrome

In a group of 177 patients with COPD who underwent home sleep studies, 20% had apnea hypopnea indices greater than 10 events/hour, and this group had a higher BMI and greater smoking history and more arterial hypertension and diabetes than the group who did not have OSA (Steveling, 2014). Measures of arterial stiffness are greater in individuals with overlap syndrome compared with those with OSA alone and this increase is independent of nocturnal hypoxemia and systemic inflammatory markers (Shiina, 2012). The elevated arterial stiffness may contribute to increased cardiovascular comorbidities in the overlap syndrome.

Patients with overlap syndrome have higher PaCO₂ (44.59 mmHg) compared with those with either OSA (39.22 mmHg) or COPD (39.63 mmHg) which could only be partially explained by weight and airflow limitation (Resta, 2002). Patients with the overlap syndrome and daytime hypercapnia have more profound nocturnal desaturations and greater derangements in sleep quality including more apneas and hypopneas than those with normocapnia (Lopez-Acevedo, 2006).

### 11.7.2 Pulmonary Hypertension

The prevalence of pulmonary hypertension is greater among individuals with overlap syndrome compared with those with either COPD or OSA only (Rizzi, 1997; Bady, 2000; Laks, 1995; Sanner, 1997; Chaouat, 1996; Hawrylkiewicz, 2004). The diagnosis and treatment of pulmonary hypertension are discussed in Chapter 12, COPD and Pulmonary Vasculature.

### 11.7.3 Atrial fibrillation

A retrospective two year study revealed the incidence of new onset atrial fibrillation was 21% in those with the overlap syndrome compared with 10% among patients with COPD, 6% among those with OSA, and 4.9% for those with neither disorder (Ganga, 2013). Even after adjusting for comorbidities, overlap syndrome was associated with new onset atrial fibrillation, OR 3.66, 95% CI 1.056, 6.860. Another study showed that incident AF is associated with OSA and smoking but did not assess airflow (Gami, 2007).
11.7.4 Cognitive Dysfunction

Both COPD and OSA are associated with neurocognitive dysfunction including impaired attention, memory and learning, language and higher executive functions, and deranged visuospatial and constructional capacity (Andreou, 2014). Normally, cerebral blood flow (CBF) increases during episodes of arterial hypoxemia to protect the brain from neuronal injury but this compensatory mechanism is lost during non-rapid eye movement sleep (Alexancre, 2014). Thus, this loss of compensatory CBF during sleep may contribute to enhanced hypoxemia-induced neuronal injury and increased cognitive dysfunction in the overlap syndrome. Cognitive function in the overlap syndrome has not been well studied but, since hypoxemia is believed to be the major factor contributing to poor performance, these impairments may be more pronounced in individuals with overlap syndrome.

11.8 Mortality and COPD Exacerbations

The leading cause of death among patients with the overlap syndrome is cardiovascular disease (Marin, 2010; McNicholas, 2009). Among patients with OSA, mortality is associated with concurrent COPD, OR, 7.07, 95% CI 2.75–18.16 (Lavie, 2007). Conversely, mortality is increased in individuals with COPD and untreated OSA compared with those with the same severity of COPD and no OSA (Marin, 2010). Patients with overlap syndrome not treated with CPAP have a higher mortality, relative risk (RR) 1.79, 95% CI 1.16, 2.77, and greater risk of a COPD exacerbation requiring hospitalization, RR 1.70, 95% CI 1.21–2.38 compared with patients with COPD after adjusting for age, sex, body mass index, tobacco and alcohol use, comorbidities, COPD severity, AHI, and daytime sleepiness (Marin, 2010).

11.8.1 Treatment

In general, there is no specific treatment for the overlap syndrome and management is directed toward the two underlying disorders, COPD and OSA, and associated comorbidities.

11.8.2 Respiratory Medications

Therapy for COPD is discussed in Chapter 14, Management of Stable COPD. Both short and long acting anticholinergics improve nocturnal oxygenation and sleep quality in patients with COPD (Martin, 1999; McNicholas, 2004). In patients with OSA alone, the mean SpO2 and duration of time with SpO2 ≤90% are reduced after treatment with sal-
meterol but total sleep time, quality of sleep, and AHI were unchanged (Rasche, 1998; Rasche, 1999). The proportion of respiratory symptom free nights increase in patients with COPD treated with high dose but not low dose combined LABA/ICS and with LABA alone (Tashkin, 2012). The proportion of patients with stable COPD who have insomnia is less in those treated with a beta agonist, either albuterol or formoterol, or with a long acting inhaler, either tiotropium or formoterol (Budhiraja, 2012).

Some treatments for COPD may reduce sleep quality. Systemic corticosteroids are associated with an increased risk of insomnia in individuals with COPD (Wood-Baker, 2005; Aaron, 2003). In addition, prolonged or recurrent, intermittent use of steroids may cause weight gain, a risk factor for OSA, and steroid myopathy which might reduce respiratory muscle strength further worsening hypoventilation during sleep (Mieczkowski, 2014).

Despite its benefits on physical conditioning, quality of life, anxiety, and depression, the effect of pulmonary rehabilitation on sleep quality in patients with COPD is not clear with some studies demonstrating improvement and others showing no effect (Lan, 2014; McDonnell, 2014).

### 11.8.3 Oxygen

Oxygen improves survival in individuals with COPD and resting hypoxemia despite optimized medical management (reviewed in Chapter 14, Management of Stable COPD). The effect of supplemental oxygen for patients with COPD with resting low normal oxygenation and transient desaturations during exercise or sleep is not known. Similarly, the effect of nocturnal supplemental oxygen in individuals with OSA remains unclear. Earlier studies with small numbers of patients studied for short periods suggested that nocturnal supplemental oxygen improved sleep parameters and nocturnal oxygenation (Martin, 1982; Smith, 1984; Gold, 1986) but a more recent double blind, randomized trial showed that supplemental oxygen did not improve sleep parameters and only increased nocturnal oxygen levels (Loredo, 2006).

A large prospective trial comparing CPAP and oxygen treatment in individuals with OSA and cardiovascular disease or risk factors showed that CPAP but not supplemental oxygen reduced 24 hour mean arterial blood pressure; sleep parameters were not assessed but C reactive protein, a measure of systemic inflammation was only reduced with CPAP (Gottlieb, 2014).

In patients with profound nocturnal hypoxemia that is refractory to CPAP and supplemental oxygen, use of transtracheal oxygen may maintain oxygen levels during sleep (Biscardi, 2014).
11.8.4 Lung Volume Reduction Surgery (LVRS)

In patients with emphysema amenable to surgical treatment, LVRS improves sleep quality (increased total sleep time and sleep efficiency and reduced arousal index) and nocturnal oxygenation (Krachman, 2005). These benefits appear to be more related to improvements in lung mechanics, reduced air trapping and hyperinflation, than oxygenation (Krachman, 2008).

11.8.5 Noninvasive Positive Pressure Ventilation

For patients with OSA, noninvasive ventilation with positive pressure, usually continuous positive airway pressure (CPAP), is the main treatment (Epstein, 2009). In patients with the overlap syndrome, CPAP improves quality of sleep, reduces complications and mortality, and decreases COPD exacerbations (Stanchina, 2013; Marin, 2010). A retrospective review of 227 patients with overlap syndrome revealed that 17 (7.4%) died over a 3 year period; adherence with CPAP was greater in surviving patients, 65.9±1.8% of nights with > 4 hours use and mean use 5.4±0.1 hr/night, than in patients who died, 21.2±8.1% of nights with >4 hours of use and 1.7±0.2 hr/night (Stanchina, 2013). Patients with overlap syndrome not treated with CPAP have a higher mortality, RR 1.79, 95% CI 1.16, 2.77, and greater risk of a COPD exacerbation requiring hospitalization, RR 1.70, 95% CI 1.21–2.38, compared with patients with COPD after adjusting for age, sex, body mass index, tobacco and alcohol use, comorbidities, COPD severity, AHI, and daytime sleepiness (Marin, 2010). Patients with overlap syndrome treated with CPAP had the same risk of death and hospitalization for COPD exacerbations as those with COPD alone (Marin, 2010). In a study of 271 patients with overlap syndrome treated with CPAP, those with hypercapnia had less mortality than those with normocapnia, hazard ratio (HR) 0.47 (95% CI 0.23–0.89) versus 0.72 (5% CI 0.32–1.63), respectively (Jaoude, 2014). This study suggested that CPAP’s mortality benefit in the overlap syndrome occurred only in patients with hypercapnia.

In patients with obesity hypoventilation or overlap syndrome, nocturnal NIV may reduce daytime PACO$_2$ levels and this decrease is associated with less daytime somnolence and EEG activation suggesting that hypercarbia may be a contributing factor to daytime sleepiness (Wang, 2014).

A prospective randomized controlled study comparing standard therapy with or without nocturnal noninvasive ventilation in patients with stable, hypercapneic COPD for 1 year showed that, when NIV was targeted to achieved a 20% reduction in baseline PaCO$_2$ or to achieve a PaCO$_2$ less than 48.1 mmHg, mortality decreased from 33% (NIV+standard therapy) to 12% (standard therapy alone), HR 0.24 (95% CI, 0.11–0.49) (Köhnlein, 2014). A meta-analysis of NIV in patients with stable COPD showed that non-targeted routine use of NIV did not affect sleep efficiency (Struik, 2014). Thus, it appears that CPAP treatment using pressure levels determined by the
measured effect on PaCO₂ optimizes CPAP’s benefits but these studies need to be verified in a population of patients with overlap syndrome. In general, these titration studies are best performed in a monitored setting such as a sleep laboratory, measuring oxygen saturation and end tidal CO₂ levels. Bilevel noninvasive ventilation is most frequently used to augment minute ventilation and reduce PaCO₂ levels by increasing the difference between the inspiratory and expiratory pressures.

Nocturnal intelligent volume-assured pressure support noninvasive ventilation improves sleep quality and reduces PACO₂ more than high-intensity noninvasive positive pressure ventilation in patients with COPD and resting hypercapnea (Ekkem-kamp, 2014). These ventilator modes have not yet been evaluated for the overlap syndrome.

Nocturnal noninvasive ventilation may improve exercise capacity in individuals with the overlap syndrome. Walking capacity measured by the incremental shuttle walking test improves after CPAP treatment (Wang, 2013). A small study suggested that exercise tolerance measured by maximal work load during cardiopulmonary exercise testing increased in patients with overlap syndrome treated with CPAP (Nowinski, 2007).

CPAP reduces paroxysmal atrial fibrillation, sinus bradycardia, and sinus pauses among patients with OSA but its effect on these dysrhythmias in the overlap syndrome is not known (Abe, 2010).

11.9 Conclusion

Sleep disturbances may occur in up to 75% of individuals with COPD and may be due to nocturnal respiratory symptoms especially cough, sleep disordered breathing mainly OSA, or combinations of these processes. The concurrence of COPD and OSA is known as the overlap syndrome and, although its prevalence is not greater than would be predicted from the prevalence of either disorder alone, the overlap syndrome is associated with significant nocturnal hypoxemia and impaired sleep quality. This profound desaturation is due to the combined effects of COPD’s detrimental consequences on ventilation and ventilation-perfusion matching and usual hypoventilation and REM-related skeletal muscle atony. The overlap syndrome is associated with pulmonary hypertension. Treatment of the overlap syndrome includes minimizing nocturnal respiratory symptoms through optimal management of COPD, supplemental oxygen, and noninvasive positive pressure ventilation. CPAP improves sleep quality, and reduces COPD exacerbations, nocturnal desaturation, and mortality. More recent studies suggest that CPAP is mostly, and potentially only, beneficial in individuals with hypercapnia, and that use of noninvasive ventilation targeted to achieve a reduction in hypercarbia is more advantageous than non-targeted therapy.
11.10 Summary Points

1. Sleep disturbances due to nocturnal respiratory symptoms, sleep disordered breathing, or both processes occur commonly in patients with COPD.
2. Approximately 10% of individuals with COPD have OSA and the concurrence of COPD and OSA, the overlap syndrome, occurs in approximately 1% of the general population.
3. To identify sleep issues in patients with COPD, a careful and complete sleep history and sleep directed examination should be obtained.
4. Factors associated with the overlap syndrome include pulmonary hypertension, obesity, and possibly worse airflow limitation.
5. The overlap syndrome is characterized by profound nocturnal desaturation due to the combined effects of COPD and sleep on nocturnal ventilation.
6. Treatment of the overlap syndrome includes respiratory medications, supplemental oxygen, and noninvasive positive pressure ventilation.
7. Use of continuous positive airway pressure (CPAP) improves sleep symptoms, decreases COPD exacerbations, and increases survival.
8. CPAP is most beneficial in patients with overlap syndrome and hypercarbia.

References


References


Jean M. Elwing, MD

12 COPD and Pulmonary Vasculature

Key Points
1. Elevated pulmonary pressures are a common finding in patients with advanced COPD and are associated with increased morbidity and mortality.
2. Pulmonary hypertension causes progressive right ventricular hypertrophy, dilation, and dysfunction.
3. Management of COPD-related pulmonary hypertension includes treatment of underlying COPD, supplemental oxygen, and smoking cessation. Systemic vasodilators are ineffective. Pulmonary vasodilators require further study to determine their efficacy.
4. Venous thromboembolism frequently complicates COPD exacerbations. 25% of all COPD exacerbation are associated with venous thromboembolism and increase morbidity and mortality in COPD patients.

12.1 Introduction

Chronic obstructive pulmonary disease (COPD) is a multisystem chronic illness that is a major worldwide healthcare burden. It is estimated that COPD will be the fourth largest contributor to mortality by 2020 (Murray, 1997). In addition to obstructive airway disease, COPD is frequently associated with progressive pulmonary vascular disease. It is estimated that 20–65% of patients with COPD are affected by elevations in pulmonary pressures (Weitzenblum, 1984; Burrows, 1972; Oswald-Mammosser, 1987; Cuttica, 2010) with a small fraction (< 5%) having severely elevated pulmonary pressures (Thabut, 2005; Chaouat, 2005; Cuttica, 2010). Survival in COPD correlates negatively with pulmonary arterial pressures (PAP) (Oswald-Mammosser, 1995; Cuttica, 2010). Patients with COPD and pulmonary hypertension (PH) have increased morbidity and are at risk for hospitalizations for COPD exacerbations (Weitzenblum, 1984; Burrows, 1972; Barbera, 2003; Kessler, 1999). Additionally, COPD patients with PH have more severe exercise impairment (Sims, 2009; Cuttica, 2010).

COPD patients are also often affected by venous thromboembolic (VTE) disease and have a twofold increased risk of VTE as compared to other chronic medical conditions (Sidney, 2005). A systematic review of the published literature in 2009 revealed that approximately one fourth of hospitalized COPD patients presenting with dyspnea had VTE (Jacques, 2009).

Both progressive pulmonary vascular disease as well as thromboembolic disease increase morbidity and mortality in patients with COPD. This chapter will review the epidemiology of PH associated with COPD including its clinical manifestations, methods of diagnosis, pathophysiology, and treatment strategies. Additionally, this chapter will briefly discuss prevalence, impact and management of VTE in the setting of COPD.
12.2 COPD Associated Pulmonary Hypertension

12.2.1 Epidemiology

The prevalence of PH in COPD has not been accurately assessed in large epidemiologic studies because of variations in definitions of PH, limitations of accurate measurement of pulmonary pressures by echocardiogram (Fisher, 2009) as well as the risks and expense of invasive pressure measurement by right heart catheterization (RHC). To date, most studies have utilized noninvasive measures with echocardiogram to estimate pulmonary arterial pressures which provides limited insight into this condition. Some estimations of prevalence can be gleaned from limited post-mortem data and small studies evaluating pulmonary pressures by RHC. Prior to the use of supplemental oxygen and modern COPD therapy, at autopsy, approximately two thirds of chronic bronchitic patients (Millard, 1974; Scott, 1976) and one third of emphysematous patients (Leopold, 1957) have evidence of right ventricular hypertrophy supporting the ante-mortem presence of PH. In 1981, Weitzenblum evaluated 175 COPD patients’ hemodynamics with RHC and 35% were found to have elevated resting mean pulmonary artery pressures (mPAP ≥ 20 mmHg) (Weitzenblum, 1981). In 2005, hemodynamic data from 215 end-stage disease COPD patients undergoing RHC prior to lung volume reduction surgery or lung transplantation were reviewed. Pulmonary pressures were more significantly elevated in patients with end-stage pulmonary disease with more than half having a resting mPAP > 25 mmHg and approximately 15% had moderately to severely elevated pulmonary pressures (mPAP > 35 mmHg) (Thabut, 2005). Severe elevation in pulmonary pressures (>45 mmHg) is rare and most frequently found in patients with concomitant conditions contributing to PH (Thabut, 2005; Chaouat, 2005). More recently, Cuttica et al (Cuttica, 2010) retrospectively reviewed hemodynamic data from 4930 lung transplant candidates with COPD. In this cohort of patients with advanced COPD, 30.4% (1499/4930) had elevations in pulmonary pressures (mPA ≥25mmHg) of which 4.0% (196/4930) had severe PH (mPA ≥ 35mmHg) and 17% had increased left sided filling pressures. In this group, PH was associated with lower exercise capacity as well as increased mortality despite controlling for confounders such as age, ethnicity, BMI, lung function and NYHA class (Cuttica, 2010).

Resting PH associated with COPD is slowly progressive with an average increase of 0.4 mmHg per year based on data from a cohort of 131 patients followed over 6.8+/−2.9 years (Kessler, 2001). Despite slow progression of resting PH, pulmonary pressures can rise acutely with exercise (Christensen, 2004; Fujimoto, 2002), illness and sleep in COPD patients (Chaouat, 2008). Furthermore, exercise induced PH is estimated to occur in two-thirds of patients with COPD even when pulmonary pressures are normal at rest (Oswald-Mammosser, 1991; Christensen, 2004).
12.2.2 Diagnostic Evaluation

12.2.2.1 Clinical Evaluation for Pulmonary Hypertension
A thorough clinical history is important in evaluating patients with COPD and suspected PH. Other coexisting risk factors for pulmonary vascular disease should be carefully evaluated (Chaouat, 2005). History of previous VTE should be explored as a high proportion of patients experiencing COPD exacerbations also have had previous thromboembolic events (Tillie-Leblond, 2006).

Symptoms related to the development of PH in the setting of COPD may be subtle and often masked by dyspnea from obstructive lung disease (Salvaterra, 1993). Although the predictive value of specific symptoms and physical examination findings in detecting pulmonary vascular disease in a patient with COPD is not clearly elucidated, several signs and symptoms suggest the presence of PH (Salvaterra, 1993). Decreasing functional capacity with stable pulmonary function testing suggests pulmonary vascular involvement. Signs of right ventricle enlargement or overload such as the presence of a right ventricular heave, prominent P2, right sided S4 gallop, and the murmur of tricuspid regurgitation suggest the presence of PH (Salvaterra, 1993). Elevated jugular venous pressure, hepatojugular reflux, and a pulsatile liver are often signs of tricuspid insufficiency and right heart failure (Elwing, 2008).

12.2.2.2 Noninvasive Testing for Pulmonary Hypertension
Routine chest radiography may reveal prominence of the pulmonary arteries or evidence of right ventricular enlargement on lateral films. The hilar to thoracic index (distance between the right and left main pulmonary arteries divided by diameter of the chest) of > 0.36 correlates with elevated pulmonary pressures (Chetty, 1982). Additionally, enlargement of the right pulmonary artery > 16 mm or left pulmonary artery > 18 mm has been associated with elevated pulmonary pressures (Matthay, 1981).

CT chest imaging is useful to evaluate the pulmonary parenchyma in the dyspneic patient but also can reveal evidence of pulmonary hypertension. Enlargement of the main pulmonary artery > 2.9 cm correlated well with elevated pulmonary pressures in a small study of 36 patients with pulmonary hypertension due to variable causes (Tan, 1998). Furthermore, a ratio of pulmonary artery (PA) to aortic diameter > 1 was 70% sensitive and 92% specific for PH in a group of 50 patients with various etiologies of RHC proven PH (Ng, 1999). Enlarged PAs are also associated with increased COPD disease activity. In 2012 Wells et al evaluated markers associated with severe COPD exacerbations. Increased PA to aortic diameter ratio (> 1) was associated with a history of severe exacerbations as well as a predictor of future COPD events (Wells 2012). Figure 12.1.

COPD patients with associated PH frequently have electrocardiographic abnormalities consistent with right ventricular hypertrophy or strain. Additional electrocardiographic features consistent with PH include right atrial enlargement, right
axis deviation and right sided conduction abnormalities (Babera, 2003; Harrigan, 2002).

Echocardiography is the most frequent noninvasive test used to assess for PH. Pulmonary artery pressure is most frequently calculated by obtaining a maximum tricuspid regurgitant (TR) flow velocity with continuous wave Doppler and then using this value to calculate an estimated right ventricular (RV) pressure utilizing a modified Bernoulli’s equation. The peak TR velocity, v, is used to calculate the trans-tricuspid gradient, $4v^2$. The RV systolic pressure is then calculated as the sum of the trans-tricuspid gradient plus the estimated right atrial pressure (RAP) (Metz, 1987). (Figure 12.2.)

Accurate estimation of pulmonary pressures is limited by several technical factors which may be accentuated in patients with COPD due to chest wall configuration changes, air trapping and cardiac orientation in COPD (Arcasoy, 2003). Doppler echocardiographic success in estimating systolic pulmonary artery pressure in patients with COPD ranges from 26–66% (Arcasoy, 2003; Bach, 1998; Tramarin, 1991; Laaban, 1989) and often requires invasive hemodynamic assessment to confirm diagnosis of PH.

Figure 12.1: Chest CT Scan from a Patient with COPD and Pulmonary Hypertension. The pulmonary artery diameter is greater than the aortic diameter. The aorta is labeled in red with a red arrow and the main pulmonary artery (pulmonary outflow tract) is labeled in yellow with a yellow arrow.
12.2.2.3 Invasive Testing for Pulmonary Hypertension

Historical data, clinical clues, examination findings, and noninvasive testing may raise concern for the presence of pulmonary hypertension but elevated pulmonary artery pressures can only be formally diagnosed by invasive right heart catheterization with direct measurement of pulmonary pressures of ≥ 25 mmHg. Current guidelines from the Fifth World Health Organization (WHO) meeting on pulmonary hypertension include 5 subgroups of pulmonary hypertension. Pulmonary hypertension related to COPD is included in WHO Group III disease, hypoxic pulmonary hypertension (Simonneau, 2013). Right heart catheterization (RHC) is not routinely required for the evaluation of COPD patients but may be of benefit in patients with worsening dyspnea and progressive right heart failure. RHC may better delineate the etiology of symptoms and help guide management. Additionally, invasive hemodynamic data is beneficial if patients are considering lung volume reduction surgery or pulmonary transplant (Malcolm, 2008).

Figure 12.2: Echocardiogram showing flow across the tricuspid valve. Pulmonary artery systolic pressure (PASP) estimation is calculated from tricuspid regurgitant (TR) flow velocity utilizing a modified Bernoulli’s equation. The peak TR velocity, v, is used to calculate the trans-tricuspid gradient, $4v^2$. The PASP is then calculated as the sum of the trans-tricuspid gradient plus the estimated right atrial pressure (RAP). $\text{PASP} = \text{TR gradient} + \text{RA pressure (RAP)} = (4.14^2 \times 4) + 20 = 88 \text{ mm Hg}$
12.2.3 Histopathology

Histopathological changes seen in patients with COPD and associated pulmonary hypertension include pulmonary vascular changes (Hicken, 1965; Wilkinson, 1988) as well as increased RV mass (Millard, 1974; Scott, 1976). Most notable changes in the arterioles include circumferential muscular hyperplasia in the media. Additionally, the arterioles as well as the small pulmonary arteries have increased deposition of longitudinal smooth muscle (Hicken, 1965). These findings are present regardless of the use of supplemental oxygen (Wilkinson, 1988). The media of the normally poorly muscularized arterioles reveal a circular muscular coat bound by a new internal elastic lamina. Luminal narrowing is present with frequent recanalization of the arteriolar lumen (Wilkinson, 1988; Wright, 1983; Hale, 1984; Wright, 1992). In smokers, the density of the fully muscularized (0–300 μm diameter) pulmonary arteries and the thickness of the medial muscle layer is doubled and the depth of intimal fibrosis is tripled (Hale, 1984). This intimal thickening is due to both smooth muscle cell proliferation and increased elastin and collagen deposition (Santos, 2002).

12.2.4 Pathophysiology

The pulmonary vasculature of patients with COPD associated PH has abnormal intimal and medial thickening that cause luminal narrowing and obstruction of the small pulmonary arteries (Wright, 1992). These changes lead to decreased elasticity and lack of vascular recruitment (Kubo, 2000). This pulmonary vascular stiffness causes an increase in pulmonary vascular resistance (PVR) and subsequent elevation of pulmonary artery pressures (PAP). The severity of vascular abnormalities does not correlate directly with the pulmonary pressure at rest (Wright, 1992; Wilkinson, 1988). PH is slowly progressive in most patients with COPD increasing by an average of 0.4 mmHg yearly (Kessler, 2001). Eventually, PH leads to pressure overload of the right ventricle (RV). In response to pressure overload, RV muscular hypertrophy occurs (Scott, 1976; Dias, 2002; Fishman, 1976). Hypertrophy precedes contractile dysfunction of the RV (Voelkel, 2006) and is followed by a downward spiral of RV dilation, a decrease in cardiac output, and an increase in right sided filling pressures (Voelkel, 2006). Inevitably, the ability of the RV to compensate is overwhelmed and RV failure ensues.

12.2.5 Pathogenesis

The pathogenesis of the vascular abnormalities associated with COPD most likely are combined effects of hypoxia (Burrows, 1974), pulmonary dysfunction with air trapping, (Wright, 1993) and effects of smoking (Santos, 2002; Hale, 1980) leading to
inflammation (Peniado, 1999), endothelial dysfunction, (Dinh-Xaun, 1991; Peniado, 1998), and angiogenesis (Santos, 2003).

Acute hypoxemia can lead to transient increases in pulmonary vascular tone in pulmonary vascular resistance (Von-Euler, 1946; Pease, 1972). Intermittent acute hypoxemia may contribute to PH, but chronic hypoxemia likely is playing a significant role (Heath, 1973; Thompson, 1989; Vender, 1994; Reeves, 2005). The pathophysiologic mechanism of hypoxic pulmonary vasoconstriction is not fully elucidated but is likely related in part to direct action on the potassium and calcium channels (Weir, 1995), stimulation of transcription factors, (Yan, 1998; Mechtcheriakova, 1999) and release of endogenous mediators (Morrell, 1995; Chen, 1994; DiCarlo, 1995; Elton, 1992; Hu, 1998) as well as growth factors (Mechtcheriakova, 1999; Santos, 2003) triggering vasoconstriction and vascular remodeling.

Tobacco smoke is known to cause airways disease but also has a significant effect on the pulmonary vasculature. Small arterioles in smokers develop intimal changes with elastin deposition and increased collagen prior to the development of obstructive lung disease (Santos, 2002; Hale, 1980). These changes are likely related to tobacco smoke’s effects on gene expression of vasoconstrictors as well as altered nitric oxide production (Santos, 2003; Barbera, 2001; Wright, 2002; Su, 1998).

Endothelial function dysregulation in the setting of hypoxic stress (Chen, 1994; DiCarlo, 2995; Elton, 1992) and toxin exposure (Wright, 2002; Wright, 2004; Santos, 2003) plays a role in COPD associated PH (Cini, 2000; Giaid, 1993). Nitric oxide (NO), a potent vasodilating mediator with antiproliferative effects (Murad, 1997), is decreased in smokers (Barbera, 2001) and patients with COPD (Giaid, 1993). It is postulated that the reduction in NO may play a role in the development of pulmonary vascular changes in COPD related PH. Endothelin-1 (ET-1), a potent vasoconstricting (LaDouceur, 1993) and mitogenic mediator, produced by the endothelium (Dubin, 1989; Boscoe, 2000; Wedgwood, 2001) is increased in COPD (Spiropoulos, 2003) and PH (Giaid, 1993).

Various growth factors are involved in the pathogenesis of pulmonary vascular disease. Vascular endothelial growth factor (VEGF) is a growth factor that stimulates angiogenesis (Papaioannou, 2006), is increased in the pulmonary arteries of patients with COPD (Santos, 2003), and is triggered by hypoxia. Platelet derived growth factor (PDGF), a potent mitogen for smooth muscle cells (Hannink, 1989), has been demonstrated to play a role in animal models with PH (Schermuly, 2005) but no clear role has been delineated in COPD and PH to date.

The role of inflammation in COPD related PH is unclear but the degree of inflammatory infiltrate in the pulmonary vasculature does correlate with severity of intimal thickening in the pulmonary arteries (Peniado, 1999) suggesting a possible association.
12.2.6 Management of Pulmonary Hypertension

The treatment of COPD related PH requires a multimodal approach including smoking cessation, COPD management and correction of hypoxemia.

Smoking cessation and elimination of all secondhand smoke exposure is the first step in management of COPD. Because of tobacco smoke’s known adverse effect on the pulmonary vasculature (Hale, 1980; Santos, 2002), smoking cessation likely will also have a beneficial effect on pulmonary vascular disease associated with COPD.

Correction of hypoxemia with supplemental oxygen is recommended for patients with COPD as well as COPD related PH. Long-term oxygen therapy (LTOT) improves survival in hypoxic COPD patients and is associated with a mild improvement in pulmonary hemodynamics (Medical Research Council, 1981; Nocturnal Oxygen Therapy Trial Group, 1980). Furthermore, supplemental oxygen may improve exercise tolerance (Fujimoto, 2002) and may impact RV function (Olvey, 1980). LTOT has been found to slow the progression of COPD associated PH (Weitzenblum, 1985) but did not normalize pulmonary pressures (Abraham, 1968) or reverse histologic change in the pulmonary vasculature (Wilkinson, 1988).

Systemic vasodilators have been evaluated for the treatment of COPD related PH. Calcium channel blockers (CCB) have been associated with acute improvement in hemodynamics but are not effective long-term pulmonary vasodilators (Agostoni, 1989) and do not slow progression of COPD associated PH (Sturani, 1983). Furthermore, CCBs can worsen ventilation/perfusion matching (V/Q) and increase hypoxemia (Melot, 1984). CCBs are not recommended for the treatment of COPD associated PH. Hydralazine, angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blocking agents have been assessed for the treatment of COPD associated PH. These agents are ineffective (Cerda, 1985; Dal Nogare, 1986; Nong; 1996, Morrell, 2005).

Therapies targeted at pulmonary vasodilatation may play a future role in the treatment of pulmonary vascular disease associated with COPD. Currently there is limited data on the effectiveness of therapies directed at the pulmonary vasculature in COPD-related PH. Inhaled nitric oxide was tested in 2003 for outpatient treatment and it improved hemodynamics (Vonbank, 2003) but was limited by a complex delivery system and risk of worsening V/Q matching (Barbera, 1996). Phosphodiesterase inhibitors (PDEI) have been tested in small numbers of patients with COPD associated PH. PDEI prolongs the effect of NO by inhibiting the degradation of NO’s second messenger (cGMP) and promoting smooth muscle relaxation (Rabe, 1994). A study of 20 patients in 2010 revealed improved hemodynamics but worsening hypoxemia associated with the treatment of COPD associated PH with sildenafil (Blanco, 2010). Furthermore, another study of 15 patients in 2008 revealed no improvement in stroke volume or exercise capacity in COPD PH patients (Rietema, 2008). Thus, the use of pulmonary vasodilators in COPD-related PH is an area of ongoing investigation to find treatments that are effective yet safe.
12.3 COPD Associated Venous Thromboembolic Disease

12.3.1 Epidemiology of Venous Thromboembolism in COPD

COPD exacerbations are not infrequently associated with vague, nonspecific worsening of underlying breathlessness and other respiratory symptoms. 30% of exacerbations do not have a clearly documented cause. A 2009 systematic review of the literature revealed acute venous thromboembolism (VTE) complicates one of every four COPD exacerbations (Rizkallah, 2009). VTE accounts for significant morbidity among patients with COPD. This increased risk of thromboembolic disease is likely multifactorial with immobility, malignancy, and inflammation playing significant roles. In 2006, Tillie-Leblond found 25% of 211 consecutive admissions for COPD exacerbation were associated with VTE. Risk factors for VTE in this group included previous VTE, history of malignancy, and decrease in pCO₂ by > 5 mmHg (Tillie-Leblond, 2006). A 2002 French study retrospectively analyzed 50 consecutive COPD admissions with exacerbations and found that 20% had associated VTE without clearly associated risk factors. A prospective analysis at the same center also evaluated hospitalized COPD patients with increased breathlessness, no significant symptoms of infection, and a positive D-dimer. 29% of these patients had VTE. Risk factors for PE in that group were the presence of a deep vein thrombosis (DVT) and a decrease in PaO₂ by > 22 mmHg (Mispelaere, 2002).

12.3.2 Diagnostic Evaluation of Venous Thromboembolism in COPD

Venous thromboembolic disease can cause significant dyspnea, hypoxemia, and acute elevations in pulmonary pressures. Large thrombus burden or events in patients with advanced cardiopulmonary disease can produce right heart dysfunction, hypotension, shock, and death (Tapson, 2008).

Clinical evaluation of COPD patients presenting with acute onset of dyspnea should begin with a thorough history. Lack of infective symptoms should raise the suspicion for non-infectious causes of the COPD exacerbation. Physical examination should include assessment for findings consistent with obstructive airways disease including wheezing, decreased breath sounds, or prolonged expiratory phase. The lack of these features, should also prompt further assessment of alternative etiologies of dyspnea including VTE. If the examination reveals clinical findings consistent with elevated pulmonary pressures and right heart failure (including RV heave, TR murmur, RV gallop, hepatojugular reflux, jugular venous distention, ascites or edema), concern for VTE should be heightened.

D-dimer may be a useful laboratory test in the outpatient setting to assess patients with COPD with increased dyspnea. D-dimer antigen is a marker of fibrin degradation (Adam, 2009) and is frequently used to evaluate select patients for the presence
of VTE (Wells, 2001). Unfortunately, D-dimer positivity can be seen in multiple conditions and is not a reliable tool in patients with other conditions including renal failure, surgery, cancer, sepsis, and normal pregnancy (Rathbun, 2004).

VTE encompasses all thromboembolic diseases including DVT and pulmonary embolism (PE). Currently, multi-detector computed tomography pulmonary angiography (CTPA) is the best imaging study for the diagnosis of acute PE (Mos, 2012; Klok, 2011). This technique has both high sensitivity, 96–100%, and specificity, 97–98% (Remy-Jardin, 2007). Unfortunately, the use of intravenous contrast may be contraindicated in patients with allergies to iodinated contrast and those with renal insufficiency or who are at risk for contrast-induced nephropathy.

In patients are unable to undergo CTPA, ventilation perfusion scintigraphy (V/Q) is the next best imaging procedure for acute PE (Mos, 2012). Results of V/Q scanning require correlation with clinical presentation for interpretation (PIOPED, 1990). Known pulmonary parenchymal and airways disease in patients with advanced COPD may increase the difficulty of interpretation. Up to half of patients with suspected PE may have intermediate scans and require further testing to exclude or establish a diagnosis of PE (Anderson, 2007).

12.3.3 Management of Venous Thromboembolism in COPD

VTE should be considered in any COPD patient presenting with dyspnea. If VTE is detected, full dose anticoagulation is indicated as per current guidelines without delay (Guyatt, 2012). Patients who do have VTE with COPD have poor outcomes. In the RIETE registry, an ongoing international multicenter prospective cohort of consecutive patients with symptomatic objectively confirmed acute VTE, COPD patients with concomitant VTE have a threefold increase in mortality (11%) compared with those patients who do not have VTE (Bertoletti, 2013). Patients should be treated with anticoagulation according to the most recent guidelines (Guyatt, 2012). Patient should be monitored closely after discontinuation as affected individuals have higher risk of recurrent disease.

12.4 Summary

Pulmonary vascular disease including chronic progressive pulmonary vascular changes leading to pulmonary hypertension as well as acute venous thromboembolic disease has a severe negative effect on the outcomes of patients with COPD. Pulmonary hypertension is a common feature of advanced COPD and is estimated to affect ≥ 20% of patients with advanced COPD (Weitzenblum, 1981; Schraf, 2002; Oswald-Mammosser, 1991). The vast majority of PH associated with COPD is mild to moderate (mPAP 20 – 35 mmHg) with severe PH (mPAP ≥ 40 mmHg) occurring in
<5% of patients with COPD (Chaouat, 2005). Elevated pulmonary pressures correlate with an increased risk of exacerbations and hospitalizations for COPD (Kessler, 1999). Severe PH in patients with COPD reduces median survival by approximately 40 months (Chaouat, 2005). The pathogenesis of PH associated with COPD has not been clearly elucidated but is likely due to the combined effects of inflammation (Peinado, 1999), endothelial cell dysfunction (Dinh-Xaun, 1991; Peinado, 1998), and angiogenesis (Santos, 2003) that lead to intimal thickening, luminal narrowing, and arteriolar muscularization (Barbera, 1994; Peinado, 1998; Magee, 1988; Hale, 1980). Smoking cessation, COPD management and oxygen therapy are recommended for management. Long-term oxygen therapy is a proven therapy for COPD and is associated with slowing progression but not resolution of associated PH (Medical Research Council, 1981; Nocturnal Oxygen Trial Group, 1980). Systemic vasodilators are not effective therapy in COPD related pulmonary hypertension (Sturani, 1983). Selective pulmonary vasodilators require further study to determine if they may be of benefit to patients with COPD and PH. VTE is another serious pulmonary vascular complication of COPD. It is associated with a three-fold increase in mortality in COPD patients. A high index of suspicion for VTE with prompt evaluation and treatment initiation is recommended. Further study is required to better understand the etiology, pathophysiology, and optimal management of patients with COPD and concomitant VTE.

12.5 Summary Points

1. The prevalence of PH among individuals with COPD increases with airflow obstruction severity; approximately 20% of patients with advanced COPD have PH.
2. The vast majority of PH associated with COPD is mild to moderate (mPAP 20–35 mmHg); severe PH (mPAP ≥ 40 mmHg) occurs in <5% of patients with COPD.
3. Elevated pulmonary pressures correlate with increased risk of COPD exacerbations and hospitalizations.
4. Severe PH in patients with COPD reduces median survival by approximately 40 months.
5. Treatment of COPD-related PH includes smoking cessation, COPD management, and supplemental oxygen therapy.
6. Systemic vasodilators are not effective therapy in COPD related PH.
7. Selective pulmonary vasodilators require further study to determine if they may be of benefit to patients with COPD and PH.
8. VTE is another serious pulmonary vascular complication of COPD and occurs in approximately 25% of patients hospitalized for COPD exacerbations.
References


References


Key Points
1. COPD profoundly affects patients’ psychosocial functions and these adverse effects may deleteriously affect a patient’s perception and response to COPD’s respiratory manifestations.
2. The prevalence of depression, anxiety, and panic disorders is markedly increased in individuals with COPD.
3. Depression and anxiety are associated with increased healthcare utilization and morbidity and mortality.
4. Panic disorders may impair patients’ ability to react to and treat acute exacerbations of COPD.
5. Cognitive dysfunction may impair the ability to use or adhere with respiratory treatments, daily function, and interpersonal relationships.
6. The familial and social networks of patients with COPD are frequently reduced and interpersonal relationships are strained, causing stress for all parties.
7. Pulmonary rehabilitation reduces anxiety and depression associated with COPD.

13.1 Introduction

COPD is associated with psychosocial disorders including depression, anxiety, panic attacks, and cognitive impairment as well as alterations in interpersonal relationships (Fan, 2014). These psychological comorbidities may worsen the underlying disease, alter the perception of respiratory symptoms, and may affect self-management of COPD (DeJean, 2013). Cognitive impairment may affect a patient’s ability to understand or remember medications or appointments. Changes in social interactions may lead to social isolation, spousal or familial conflict, and may affect psychological manifestations of COPD. Although profound psychosocial alterations may accompany COPD, these processes have only recently been comprehensively studied and optimal approaches to treatment are still under evaluation.

13.2 Depression

Depression is an altered mood characterized by a loss of interest or pleasure in life’s activities (American Psychiatric Association, 2013). The Diagnostic and Statistical Manual (DSM) IV criteria for major depression are presented in Table 13.1. Measures of depression in patients with COPD include the Beck Depression Inventory, the Center
for Epidemiological Studies Depression Inventory, the Patient Health Questionnaire Depression Scale, and the Hospital Anxiety and Depression Scale (Beck, 1978; Radloff, 1977; Kroenke, 2001; Zigmond, 1983).

### 13.2.1 Prevalence

The prevalence of depression among individuals with COPD ranges from 7–88% and depends upon the sample population of patients with COPD, airflow limitation severity, and the diagnostic tool(s) used to define depression (Yohannes, 2010; Hyninnen, 2005; Putman-Casdorph, 2009). COPD increases the risk of concurrent depression, relative risk (RR) 1.69 [95% confidence interval (CI) 1.45–1.96] and depression increases the risk of mortality in those with COPD, RR 1.83 [95% CI 1.00–3.36] (Atlantis, 2013). A meta-analysis revealed an odds ratio (OR) of 2.8 for depression among individuals with COPD compared with healthy controls (Zhang, 2011). A 2013 meta-analysis of 6 studies showed that COPD is associated with an increased risk of depression, RR 1.69 [95% CI 1.45-1.96] (Atlantis, 2013).

Only one third of patients with COPD and high depression scores have been diagnosed with treatment relevant depression and only 22% have been treated (Hanania, 2011). The estimated annual care cost for patients with COPD and associated depression or anxiety is $28,961 versus $22,512 for COPD alone (Dalal, 2011).

A review of 38,010 patients with a new diagnosis of COPD from 2000–2004 compared with matched controls in Taiwan demonstrated that incident depression was 1.88 fold greater in those with COPD (12.2 versus 6.47 per 1000 person years) and

### Table 13.1: DSM-IV Criteria for Major Depressive Disorder (APA, 2013)

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<th>Criteria for Major Depressive Disorder</th>
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<tr>
<td>Depressed mood or a loss of interest or pleasure in daily activities for more than two weeks.</td>
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<tr>
<td>1. Mood represents a change from the person’s baseline.</td>
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<td>2. Impaired function: social, occupational, educational.</td>
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<td>3. Specific symptoms, at least 5 of these 9, present nearly every day:</td>
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<td>4. Depressed mood or irritability most of the day, nearly every day, as indicated by either subjective report (e.g. feels sad or empty) or observation made by others (e.g. appears tearful).</td>
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<tr>
<td>5. Decreased interest or pleasure in most activities, most of each day</td>
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<td>6. Significant weight change (5%) or change in appetite</td>
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<td>7. Change in sleep: Insomnia or hypersomnia</td>
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<td>8. Change in activity: Psychomotor agitation or retardation</td>
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<td>9. Fatigue or loss of energy</td>
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<tr>
<td>10. Guilt/worthlessness: Feelings of worthlessness or excessive or inappropriate guilt</td>
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<tr>
<td>11. Concentration: Diminished ability to think or concentrate, or more indecisiveness</td>
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<tr>
<td>12. Suicidality: Thoughts of death or suicide, or has suicide plan</td>
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that the diagnosis of depression was greatest in the year after COPD diagnosis and declined thereafter (Tsai, 2013). Younger women, lower socioeconomic status, hospitalization, and comorbidities (hypertension, arthritis, cancer, and cardiovascular disease) were associated with an increased diagnosis of depression (Tsai, 2013).

In another group of 245 patients with COPD, 17.6% had depression defined by a Centers for Epidemiologic Studies Depression (CES-D) scale of 24 or higher and the presence of depression increased with the BODE quartile but did not correlate with COPD severity measured by GOLD stage (Kim, 2014). The level of education was inversely correlated with the prevalence of depression (Kim, 2014).

In a group of 307 patients with COPD, 12.4% had anxiety, 9.1% had depression, and 16.3% had both anxiety and depression measured by the Hospital Anxiety and Depression Scale (HADS) (Hilmarsen, 2014). Anxiety and depression scores correlated with COPD Assessment Test (CAT) scores, a disease-specific health status survey, but not with updated GOLD scores (Hilmarsen, 2014). In contrast, others have found a higher prevalence of anxiety and depression in patients with former GOLD stage IV compared with stages I and II (Janssen, 2010) and among patients with greater respiratory symptoms (updated GOLD groups B and D) (Lee, 2013).

13.2.2 Manifestations

Manifestations of depression in patients with COPD include poor self-reported health status, feelings of hopelessness and pessimism, poor sleep quality and quantity (see Chapter 11, COPD and Sleep), reduced appetite, concentration, and social interactions, fatigue, and lassitude (Felker, 2001; Emery, 2008). Depression may be associated with increased somatization and heightened awareness and sensitivity to respiratory symptoms. Depression and activities of daily living appear to be more important determinants of quality of life than severity of airflow impairment (Yohannes, 1998). Functional impairment, disability, and health status are worse for depressed patients with COPD compared with those who do not have depression and functional capacity may be more highly correlated with depression than severity of pulmonary physiologic impairment (Graydon, 1995; Yohannes, 1998; Yohannes, 2005; Felker, 2001; Kim, 2000). Individuals with COPD and depression are less likely to utilize self-management strategies or healthy behaviors such as smoking cessation compared with those who are not depressed (Stapleton, 2005; Dowson, 2004; Wagena, 2004).

Higher anxiety and depression levels are associated with greater fatigue, breathlessness, and frequency of respiratory symptoms among patients with COPD (Doyle, 2013). Depression, along with poor health status and COPD severity, is a key predictor of reduced physical activity (a key prognostic indicator in COPD) measured by walking less than 30 minutes daily (Miravitlles, 2014). In contrast, others have shown that depression is associated with poorer quality of life but not reduced activities of daily living (Weldam, 2013). A meta-analysis of studies evaluating depression and
quality of life among individuals with COPD and airflow limitation confirmed by spirometry showed that depression significantly correlated with health related quality of life, pooled $r=0.48$, 95% CI 0.37–0.57 (Blakemore, 2014).

Individuals with COPD have twice the prevalence of insomnia (adjusted odds ratio (aOR), 2.4) compared with the general population and nearly half (48.1%) of individuals with COPD have insomnia (Ohayon, 2014). Most individuals with COPD and depression (84.4%) or anxiety (59.7%) had associated insomnia symptoms (Ohayon, 2014). Co-occurrence of insomnia and depression or anxiety was associated with a five-fold increase of hospitalization for COPD and a reduced quality of life (Ohayon, 2014).

13.2.3 Mortality

Depression is a risk factor for mortality in individuals with COPD (Atlantis, 2013; Yohannes, 2005; de Voogd, 2009). A meta-analysis of 16 studies following 28,759 individuals with COPD for 1 to 8 years showed that depression was associated with increased mortality, RR 1.43 [95% CI, 1.00–3.36] (Atlantis, 2013). Among 100 patients hospitalized for acute exacerbations of COPD, 56% had depression, and depression was associated with an increased one year mortality, OR 1.13 [95% CI, 1.02–1.26] (Yohannes, 2005). Depression was associated with a greater mortality, OR 1.93 [95% CI, 1.12–3.33], among 121 patients with COPD who completed inpatient pulmonary rehabilitation and were followed for 8.5 years (de Voogd, 2009).

13.2.4 Healthcare Utilization

Anxiety and depression are significant factors associated with admissions and re-admissions for COPD exacerbations. Other factors include: reduced quality of life, COPD severity, female sex, lower BODE scores, persistent smoking, increased breathlessness, hypercapnea, hypoxemia, long term oxygen use, sense of loss, inability to cope, decrease in self-efficacy, poor adherence to therapy, lower socioeconomic status, and prior COPD exacerbations (Pooler, 2014). Depression may reduce an individual’s motivation to seek assistance either medically or socially.

A 2012 meta-analysis of nine prospective studies showed that, among individuals with COPD, the number of exacerbations requiring hospitalization was increased in those with concurrent depression (RR 1.12, 95% CI 1.02–1.24) and both anxiety and depression (RR 1.18, 95% CI 1.01–1.38) but not with anxiety alone (RR 1.05, 95% CI 0.92–1.19) (Laurin, 2012). A subsequent 2013 meta-analysis of 13 studies showed that anxiety or depression were associated with an increased risk of adverse COPD-related outcomes (RR 1.43, 95% CI 1.22–1.68) and that depression increased the risk of mortality (RR 1.83, 95% CI 1.00–3.36) (Atlantis, 2013).
Anxiety and depression are associated with activation of the hypothalamic-pituitary-adrenal axis and increased systemic inflammation (Cameron, 2004; Ehlert, 2001; Bremmer, 2008; Joynt, 2004). Anxiety and depression are also associated with low self-confidence or self-efficacy which may detrimentally affect a number of health care activities including physical activity, medication adherence, smoking cessation, healthful nutrition, and pulmonary rehabilitation engagement (Laurin, 2012).

13.2.5 Management

Increased disease knowledge, self-efficacy, and better perceived social support are associated with fewer depressive symptoms in individuals with COPD (Lee, 2013). Problem-oriented coping strategies that focus on eliminating the source of the stress or learning how to best cope with the stressor may translate into a better understanding of COPD into less depressive symptoms and may provide a mechanism of intervention to alleviate psychological symptoms of COPD (Lee, 2013). Controlled breathing techniques (relaxation exercises, pursed-lip breathing, and active expiration) taught by respiratory therapists may reduce breathlessness, anxiety, and depression in patients hospitalized with COPD exacerbations (Valenza, 2014). Systemic review of randomized controlled trials of psychological and or lifestyle interventions for individuals with COPD showed that exercise training was the only intervention associated with significant treatment effects for depression and anxiety (Coventry, 2013).

13.2.5.1 Pharmacologic Treatment

Antidepressants have not been shown to induce remission of depression or to reduce respiratory symptoms in individuals with COPD (Yohannes, 2014). A review of pharmacologic treatment of depression in COPD analyzed six studies of selective serotonin reuptake inhibitors and four trials of tricyclic antidepressants and concluded that there is no conclusive evidence for the efficacy of any antidepressant in this patient population (Yohannes, 2014). In a retrospective analysis of 17,320 Medicare beneficiaries with COPD, 86.8% of those with concurrent depression were receiving antidepressant treatment, and treatment was associated with lower mortality, hazard ratio (HR) 0.55 [99% CI, 0.44–0.68] (Qian, 2013). Further studies are required to determine the efficacy and optimal class of antidepressant for the management of depression in individuals with COPD.

13.2.5.2 Pulmonary Rehabilitation

Pulmonary rehabilitation reduces levels of anxiety and depression for individuals with all levels of COPD severity (Tselebis, 2013; Emery, 1998; Griffiths, 2000; Guell, 2006; Guell, 2006; Withers, 1999; Hui, 2003). Individuals who do not complete pul-
Pulmonary rehabilitation have higher rates of depression and somatization measured by the SCL-90 compared with those who complete rehabilitation (Tselebis, 2014). Pulmonary rehabilitation participants with anxiety and or depression are 10 fold more likely not to achieve the minimal clinically important difference improvement in breathlessness (Hornikx, 2013).

13.3 Anxiety

Anxiety is an apprehensive anticipation of danger or stressful situations associated with increased nervousness or worry (APA, 2013). The DSM-IV criteria for the diagnosis of Generalized Anxiety Disorder are presented in Table 13.2. Anxiety disorders associated with COPD include generalized anxiety disorder (6–33%), panic disorder (with or without agoraphobia) (0–41%), specific phobia (10–27%), and social phobia (5–11%) (Willgoss, 2013). The Anxiety Inventory for Respiratory Disease (AIR) is a COPD-specific nonsomatic anxiety scale that can be used to screen for and measure anxiety in individuals with COPD and correlates well with the Hospital Anxiety and Depression-Anxiety subscale (Willgoss, 2013). Other anxiety measures include the Beck Anxiety Inventory, the State-Trait Anxiety Inventory, and the Hospital Anxiety and Depression Scale (Beck, 1988; Spielberger, 1970; Zigmond, 1983). Surveys that include screens for somatic complaints such as shortness of breath and tiredness tend to overestimate the prevalence of anxiety among individuals with COPD because of the overlap of symptoms between anxiety and COPD (Mikkelsen, 2004).

Table 13.2: DSM-IV Criteria for the Diagnosis of Generalized Anxiety Disorder (APA, 2013)

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<th>Criteria for Generalized Anxiety</th>
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<tr>
<td>At least 6 months of “excessive anxiety and worry” about a variety of events and situations. Generally, “excessive” can be interpreted as more than would be expected for a particular situation or event. Most people become anxious over certain things, but the intensity of the anxiety typically corresponds to the situation.</td>
</tr>
<tr>
<td>There is significant difficulty in controlling the anxiety and worry. If someone has a very difficult struggle to regain control, relax, or cope with the anxiety and worry, then this requirement is met.</td>
</tr>
<tr>
<td>The presence for most days over the previous six months of 3 or more (only 1 for children) of the following symptoms:</td>
</tr>
<tr>
<td>1. Feeling wound-up, tense, or restless</td>
</tr>
<tr>
<td>2. Easily becoming fatigued or worn-out</td>
</tr>
<tr>
<td>3. Concentration problems</td>
</tr>
<tr>
<td>4. Irritability</td>
</tr>
<tr>
<td>5. Significant tension in muscles</td>
</tr>
<tr>
<td>6. Difficulty with sleep</td>
</tr>
<tr>
<td>The symptoms are not part of another mental disorder.</td>
</tr>
</tbody>
</table>
13.3.1 Prevalence

The reported prevalence of anxiety among individuals with COPD ranges widely from 2–100% and depends upon the sample population of patients with COPD, airflow limitation severity, and the diagnostic tool(s) used to define anxiety (Brenes, 2003; Mikkelsen, 2004; Yohannes, 2010; Hynninen, 2005; Putman-Casdorph, 2009). The prevalence of anxiety ranges from 10–55% in hospitalized patients to 13–46% among outpatients with COPD and is greater among women than men (Willgoss, 2013).

Anxiety is related to depression in individuals with COPD; 37% of those patients with COPD and depression have anxiety, whereas only 5% of nondepressed individuals have anxiety (Yohannes, 2000). In a study of 45 Veterans with COPD, anxiety and depression scores were highly correlated and all participants with mild or moderate anxiety also had depression (Light, 1985). Greater use of catastrophic coping strategies, higher levels of negative social support, and lower levels of symptom self-management are associated with greater anxiety among men with COPD whereas higher levels of positive social support are associated with less anxiety (McCathie, 2002). Anxiety levels are associated with greater social isolation (Lustig, 1972). A meta-analysis of studies evaluating anxiety and quality of life among individuals with COPD and airflow limitation confirmed by spirometry showed that anxiety significantly correlated with health related quality of life, pooled r=0.36, 95% CI 0.23–0.48 (Blake-more, 2014).

Anxiety levels in individuals with COPD are higher in women than men, current smokers than nonsmokers, and those with marital dissatisfaction (Ashmore, 2005; Gudmundsson, 2006). Most, but not all, studies suggest that anxiety levels do not correlate with levels of resting or exertional breathlessness, airflow limitation severity, or other pulmonary physiologic impairments (Garuti, 2003; Gudmundsson, 2006; Hajiro, 2000; Wagena, 2005; Engstrom, 1996; Dowson, 2001). The relationship between breathlessness and anxiety is unclear but Bailey has proposed a “dyspnea-anxiety-dyspnea” cycle that suggests that anxiety does not cause breathlessness but is a sign of dyspnea (Bailey, 2004).

Levels of anxiety do not correlate with pulmonary physiology or 12 minute walking tests (Light, 1985). Anxious individuals experience more symptoms of nicotine withdrawal upon smoking cessation and, therefore, may have a higher predilection to nicotine addiction due to increased difficulty in stopping smoking (Breslau, 1992; Hill, 2008).

In patients presenting to the emergency department with respiratory exacerbations of asthma or COPD, the presence of anxiety and or depression correlated with hospitalization and relapse within 30 days (Dahlen, 2002). Among patients hospitalized with a COPD exacerbation, greater anxiety is associated with a higher risk of rehospitalization within 12 months, HR 1.07, 95% CI 1.03–1.11, per 4 unit increase in the hospital anxiety and depression scale (Gudmundsson, 2005). In contrast, a study of 43 Veterans showed that anxiety and depression were associated with poor func-
Anxiety status but not with inpatient or outpatient healthcare utilization (Kim, 2000). Poor emotional functioning measured by the chronic respiratory questionnaire portends higher mortality in women with COPD who live alone and are prescribed long-term oxygen (Crockett, 2002).

13.3.2 Manifestations

Manifestations of anxiety in patients with COPD include muscle tension, breathlessness, chronic worry, palpitations, feeling on edge, nausea, numbness, and fear of losing control (Emery, 2008). Anxiety correlates with quality of life in patients with COPD (Brenes, 2003). Many individuals with COPD and anxiety experience panic attacks (see Panic Attack section below).

13.3.3 Management of Anxiety

13.3.3.1 Pharmacotherapy

Two trials of buspirone, a serotonin receptor agonist, yielded mixed results, whereas citalopram, a selective serotonin reuptake inhibitor, was not effective in treating anxiety in patients with COPD (Argyropoulou, 1993; Singh, 1993; Silvertooth, 2004). Nortriptyline, a tricyclic antidepressant, effectively reduced both anxiety and depression (Borson, 1992). Due to a paucity of studies, a 2011 Cochrane analysis was not able to determine whether pharmacological treatment of anxiety disorders in individuals with COPD was effective (Usmani, 2011).

13.3.3.2 Nonpharmacotherapy

Psychotherapy has yielded mixed results for the treatment of anxiety in pulmonary rehabilitation programs (Lustig, 1972; de Godoy, 2003; Renfroe, 1988). A systemic meta-analysis of psychologically based interventions for the psychological manifestations of COPD showed benefit that was limited to anxiety (Baraniak, 2011). A qualitative study of 14 individuals with COPD and self-reported symptoms of anxiety revealed intense thoughts of fear, hopelessness, and confusion that were associated with anxiety and panic attacks and ameliorated with self-talk coping strategies (Willgoss, 2012). Progressive muscle relaxation techniques do not reduce anxiety in patients with COPD (Renfroe, 1988; Gift, 1992; Sassi-Dambron, 1995). Participation in comprehensive pulmonary rehabilitation reduces anxiety in patients with COPD (Emery, 1991; Griffiths, 2000; Guell, 2006; Kayahan, 2006; Emery, 1998).
Panic attack is defined as a brief period of intense fear or discomfort in which four or more of 13 symptoms (listed in Table 13.3) develop abruptly and reach a peak within 10 minutes (Craske, 2010). Panic disorder is defined as recurrent panic attacks, at least one of which has been followed by one month of any or all of persistent concern about having additional attacks or their consequences; worry about the implications of the attack or its consequences or a significant change in behavior related to the attacks; the panic attacks are not due to the direct physiological effects of a substance or a general medical condition; the panic attacks are not better accounted for by another mental disorder (Craske, 2010). In individuals with COPD, panic disorder can only be diagnosed when the panic attacks are not cued by internal stressors such as respiratory infections triggering COPD exacerbations or by external stressors such as exertion (Livermore, 2010).

### Prevalence

Depending upon the population of COPD patients sampled and the method and threshold for defining and identifying panic attacks and panic disorder, between 6.5 and 67% of patients with COPD have a diagnosis of panic disorder (Weaver, 1997; Kim, 2000; Patten, 2007; Hallas, 2009; Kunik, 2005; Pollack, 1996; Livermore, 2010).
In a study of hospitalized patients with COPD, 73% of those with an anxiety disorder had panic disorder with agoraphobia (Voegele, 2008). Conversely, the lifetime prevalence of respiratory disorders is greater in patients with panic disorder (47%) compared with those with obsessive-compulsive disorder (13%) or eating disorders (13%) (Zanderbergen, 1991) and more patients with panic disorders have respiratory diseases, especially bronchitis, than those with other anxiety disorders, 42.7 versus 16.2% (Verburg, 1995A). Over 12 months, 63% of individuals with COPD experience at least one panic attack and, when surveyed, 37–51% have had a panic attack in the prior 3–4 weeks (Porzelius, 1992; Howard, 2009). Elderly women with COPD report more panic attacks than those without COPD, OR 4.13 [95% CI, 2.65–6.43] (Smoller, 2003). A large European telephone survey of 10,854 adults reported an adjusted odds ratio of 7.1 for panic disorder among those with COPD compared with those who did not have COPD (Ohayon, 2014). Predictors of panic-spectrum psychopathology in individuals with COPD include more severe depressive symptoms, greater catastrophic interpretations of shortness of breath, greater anxiety sensitivity, and degree of recent life stressors, and lower FEV₁ (Livermore, 2012). Individuals with COPD and panic disorder have a heightened sensation of breathlessness during inspiratory load testing compared with age-matched individuals with similar levels of airflow limitation and COPD (Livermore, 2008; Giardino, 2010). This increased sensation of dyspnea appears to be due to heightened emotional responses to breathlessness rather than increased interoceptive sensitivity (Giardino, 2010). Patients with panic disorder experience a greater increase in subjective anxiety when exposed to 35% CO₂ than individuals with generalized anxiety disorder (Verburg, 1995B).

Individuals with COPD and panic disorder have more frequent and longer respiratory hospital admissions (Yellowlees, 1987; Gudmundsson, 2005) and greater disability and impaired function (Kim, 2000) than those without panic disorder. COPD self-management may be impaired in individuals with panic disorders (Dowson, 2004).

### 13.4.2 Treatment of Panic Disorder

Although cognitive behavioral therapy (CBT) has been demonstrated to be effective management of panic disorder in individuals who do not have COPD, its efficacy in those with COPD is less clear (Barrera, 2014; Livermore, 2010). Several studies have shown that CBT may reduce both panic attacks and respiratory hospitalizations in patients with COPD, but these studies have used different therapeutic presentations (group versus individual sessions), concurrent education and or exercise sessions, and varying durations of therapy and follow up (Livermore, 2010; Kunik, 2001; Kunik, 2007; de Godoy, 2003; Emery, 1998).

Benzodiazepines are effective treatments for panic attacks and panic disorder; however, they should be used cautiously in patients with COPD due to the potential
to blunt respiratory drive and to cause or worsen hypercapnea (Smoller, 1996). Other pharmacologic treatments for panic disorders in individuals with COPD include selective serotonin reuptake inhibitors and tricyclic antidepressants (Smoller, 1996).

13.5 Cognitive Impairment

Neuropsychological impairment may occur in individuals with COPD, especially those with hypoxemia (Dodd, 2010; Klein, 2010). The optimal screening test for cognitive function in individuals with COPD has not been determined. A study of the validity of the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) compared with a comprehensive neuropsychologic assessment in individuals with COPD showed that the MMSE did not have an acceptable cutoff and the optimal MoCA cutoff was 26 (Villeneuve, 2012).

13.5.1 Prevalence

The prevalence of cognitive dysfunction among individuals with COPD ranges from 10.4–48.5% depending upon the population studied and the methods used to detect cognitive impairment (Antonelli-Inc, 2006; Incalzi, 1993; Villeneuve, 2012; Schou, 2012). The prevalence of mild cognitive impairment among patients with moderate to severe COPD is 36% compared with 12% among healthy controls and the major impairment was nonamnestic mild cognitive impairment with attention and executive dysfunctions (Villeneuve, 2012). In a survey of 27,106 nursing home residents with COPD, 62% had short-term memory impairment and 43.3% had moderately or severely impaired daily decision making cognitive skills (Zarowitz, 2012).

Cognitive function measured by the MoCA test is more impaired among patients with acute COPD exacerbations than in those with stable COPD (Crisan, 2014). Greater deficits occurred in language abstraction and attention and delayed recall and orientation than in visuospatial and naming functions. Impairment was negatively correlated with pulmonary function and positively associated with measures of inflammation and level of CO\(_2\) (Crisan, 2014). A multivariate analysis of factors associated with cognitive impairment among individuals with stable COPD and varying levels of physiologic impairment showed that only the number of COPD exacerbations in the prior year was associated with reduced cognitive function measured by an array of standardized neuropsychological tests (Tulek, 2014).

A longitudinal study of elderly individuals showed that COPD increased the risk for nonamnestic mild cognitive impairment (NA-MCI) by 83% and that those individuals with a diagnosis of COPD for more than 5 years had the greatest risk for NA-MCI, HR 1.58 [95% CI, 1.04–2.40] (Singh, 2013; Singh, 2014). In the Cardiovascular Risk Factors, Aging, and Dementia study, a population-based longitudinal study with
25 years of follow-up, midlife COPD was associated with an increased risk for mild cognitive impairment, HR 1.85 [95% CI, 1.05–3.28] (Rusanen, 2013).

When cognitive function is measured among individuals hospitalized for acute exacerbations of COPD, 57% have impaired function, and 20% have a pathologic loss in processing speed and there was no improvement 3 months after recovery (Dodd, 2013). Cognitive function in patients with acute on chronic respiratory failure requiring mechanical ventilation is worse at hospital discharge compared with healthy controls but improves to comparable levels within six months (Ambrosino, 2002). Cognitive impairment was associated with worse quality of life measured by the St. George’s Respiratory Questionnaire and longer length of hospital stay (Dodd, 2013). Among the 432 individuals with COPD in the Cardiovascular Health Study, co-existing COPD and cognitive impairment were associated with increased respiratory-related, aHR 4.10 [95% CI, 1.86–9.05], and all cause hospitalizations, aHR 1.34 [95% CI, 1.00–1.80] and death, aHR2.29 [95% CI, 1.18–4.45] (Chang, 2012). Impaired performance on the copy with landmark test is associated with an increased mortality risk in individuals with severe COPD (Antonelli-Incalzi, 2006).

In patients with hypoxemic respiratory failure treated with supplemental oxygen, worse physiologic function measured by severity of airflow obstruction may predict those individuals who will experience cognitive decline (Incalzi, 1998). Poor adherence to medications is associated with impaired verbal memory measured by the delayed recall test (Incalzi, 1997).

13.5.2 Manifestations

Cognitive impairment may be associated with effects on day-to-day function in individuals with COPD. Driving simulation testing demonstrates increased accident frequency among individuals with COPD compared with healthy controls (Orth, 2008). Activities of daily living including self-administration of medications, continence, fiscal responsibility, and dressing correlate better with cognitive function than with lung physiologic function in individuals with COPD (Antonelli-Incalzi, 2008). Further, impaired cognitive function correlates with inability to perform technically acceptable pulmonary function testing (Allen, 2008).

Hippocampal atrophy measured by magnetic resonance imaging is associated with cognitive dysfunction and chronic hypoxemia in individuals with COPD (Li, 2013). Serum S100B levels correlate with cognitive impairment in COPD and may be a useful biomarker (Li, 2013). Among individuals with COPD, hypoxemia, \( \text{SpO}_2 < 88\% \), correlates with greater cognitive impairment, OR 5.45 (95% CI, 1.014–29.2) and the use of supplemental oxygen decreases the risk, OR 0.14 (95% CI, 0.07–0.27) (Thakur, 2010). Short term reduction of the \( \text{SpO}_2 \) to 85% by reduction of the inspired oxygen concentration in patients with COPD does not affect cognitive function measured by multiple tests suggesting that chronic rather than transient oxygen desaturation may
be critical in the development of cognitive impairment (Martin, 2011). Similarly, acute oxygen treatment does not improve neuropsychological test performance (Vos, 1995; Wilson, 1985). Longer term supplemental oxygen has either no or minimal benefits on cognitive function (Heaton, 1983; Krop, 1973; Incalzi, 1993; Hjalmarsen, 1999; Borak, 1996; Incalzi, 1993). Chronic hypoxemia combined with hypercapnia may be significant etiologic factors in the development of cognitive impairment in individuals with COPD (Zheng, 2008). Cerebral perfusion is diminished in patients with COPD and is more reduced in those with hypoxemia than in those with normoxemia and the reduction in perfusion correlates with cognitive impairment (Ortapamuk, 2006; Antonelli-Incalzi, 2003).

13.5.3 Management

Pulmonary rehabilitation and exercise may improve cognitive function among individuals with COPD (Etnier, 2001; Angevaren, 2008; Emery, 2008). Acute and prolonged (10 weeks) exercise improves performance on the Verbal Fluency test (Emery, 2001; Emery, 1998). Individuals who maintain an exercise regimen after pulmonary rehabilitation sustain improvements in cognitive and psychological function, whereas those who stop exercising lose the benefits of rehabilitation (Emery, 2003). Lung volume reduction surgery may be associated with six month improvements in visuomotor speed that are not sustained one or two years after surgery (Kozora, 2008; Kozora, 2011). Cognitive training is not effective in improving cognitive function in individuals with COPD (Incalzi, 2008).

13.6 Social Interactions

The effect of COPD on social interactions has only recently been investigated. In older individuals, negative social interactions have greater effects than positive interactions (Newsom, 2005). Perceived negative social support is associated with higher levels of anxiety and depression among patients with COPD, whereas positive social support correlates with less anxiety and depression (McCathie, 2002). Individuals with COPD often experience a shrinking social network and nearly one third of Veterans with COPD felt social and familial isolation due to respiratory limitations on activities and concern for developing respiratory symptoms or distress with activities or interactions (Panos, 2013). Individuals with COPD who are homebound have increased risk of hospitalization during the winter in the United Kingdom (Jordan, 2008) and those with reduced social support have a 50% increased risk of hospital admissions for COPD (Partridge, 2011). Patients with COPD who are single have an 18% higher admission rate for COPD exacerbations than those individuals with a supporting spouse (Wong, 2008). Socio-economic deprivation measured by the Scot-
tish Index of Multiple Deprivation (a weighted index of seven domains: employment, income, crime, housing, health, education, and access) correlates with the frequency of hospital admissions for COPD (McAllister, 2013). Negative social support, perceived insensitive and unsympathetic responses by social network members and perception that their social network let them down when needed, and receipt of instrumental support, receiving aid or assistance from others, are associated with greater anxiety among patients with COPD. Negative social support may foster fears of social isolation and rejection whereas instrumental support may realize an individual’s needs and dependence upon others (DiNicola, 2013).

A higher perceived level of social support correlates with better overall functioning in depressed elderly with COPD (Marino, 2008). Positively perceived social support is associated with fewer hospitalizations and COPD exacerbations, improved quality of life, and increased self-efficacy for including participation in health-promoting activities such as smoking cessation and physical activity (Harris, 2007; Lee, 1991; Murray, 1995).

### 13.7 Effect of COPD on Caregivers

Until recently, the effect of COPD on caregivers has not been fully examined, interventions to improve COPD management have largely ignored nonhealthcare providers, and economic analyses of COPD’s costs usually do not include care provided by family or others (Caress, 2009). Nearly two thirds (63.5%) of caregivers have anxiety, 34% have depression, and 27.1% have both anxiety and depression (Jacome, 2014). Perceived burden and limitation on activities, female gender, and older age were significant predictors of caregivers’ anxiety and depression (Jacome, 2014).

The number of tasks that a caregiver must supervise for an individual with COPD correlates with symptoms of depression, anxiety, interpersonal sensitivity, hostility, stress, and psychotropic medication use (Cossette, 1993). Increasing emotional support caused the greatest stress on caregivers (Cossette, 1993). The burden felt by caregivers of individuals with COPD was greater among younger caregivers and did not correlate with gender, education, perceived financial capability, or employment status (Cain, 2000). In interviews of women caring for husbands with COPD, Bergs (Bergs, 2002) found that the women were dissatisfied with their recreation, lack of support from other family members, friends, and the healthcare system; they desired more information and support from healthcare providers, recognition of their caring role, and opportunities for respite care. Less positive and more negative dyadic coping (methods of dealing with stress within a couple) are associated with greater psychological stress including anxiety and depression and lower quality of life, and the higher the patient perceived the imbalance in delegated dyadic coping, the lower the couple’s quality of life (Meier, 2011). Patient marital adjustment is associated with patient well-being and partner marital adjustment is associated with patient physical...
function (Ashmore, 2005). Patients with poor marital adjustment experience greater improvements in psychological functioning after pulmonary rehabilitation than those with better marital adjustment (Ashmore, 2005). Qualitative studies of the effect of COPD on family members identified several themes: restriction in family social life, emotional distress related to COPD exacerbations, tension in couple relationships, financial strain, and coping resources (Gabriel, 2014).

Caregivers of individuals with more advanced COPD have greater subjective burden, more symptoms of depression, and worse self-rated mental health than those caring for individuals with less severe COPD; the subjective burden increased with COPD severity, depression and anxiety comorbidities, caregiver hours per week, and self-rated mental health (Fiqueiredo, 2014). As an individual with COPD’s respiratory status declines, caregiver tasks change, their relationship with the patient evolves, and they modify their expectations (Philip, 2014).

The interactions or perceptions of interactions between caregivers and individuals with COPD may affect the anxiety level. Individuals with COPD have greater anxiety levels if they perceive more insensitive and unsympathetic responses or feel that they are not supported when they need assistance or have greater anxiety levels (DiNicola, 2013). Both patients with COPD and their spouses have high and clinically significant levels of anxiety and depression and spouses who perceive patients to have higher levels of breathlessness report greater distress (Al-Gamal, 2014). They often feel powerless to relieve the breathlessness and suffering experienced by the patient (Booth, 2003; Seamark, 2004).

13.8 Conclusion

COPD is increasingly being recognized as a systemic process that affects the entire person, not only physiologically but also psychosocially. The psychological manifestations of COPD may severely affect the perception and reaction to respiratory symptoms leading to increased healthcare utilization and morbidity and mortality from COPD. The social and familial networks of individuals with COPD are often reduced and interpersonal relationships strained. Identification and management of the psychosocial manifestations of COPD is increasingly being recognized and optimal treatments are being studied.

13.9 Summary Points

1. The prevalence of depression among individuals with COPD ranges from 7–88%.
   – Depression may be associated with increased somatization and heightened awareness and sensitivity to respiratory symptoms.
Manifestations of depression in patients with COPD include poor self-reported health status, feelings of hopelessness and pessimism, poor sleep quality and quantity, reduced appetite, concentration, and social interactions, fatigue, and lassitude. Anxiety and depression are significant factors associated with admissions and re-admissions for COPD exacerbations.

Depression may reduce an individual’s motivation to seek assistance either medically or socially.

2. Anxiety occurs in 2–100% of individuals with COPD.
   - Most, but not all, studies suggest that anxiety levels do not correlate with levels of resting or exertional breathlessness, airflow limitation severity or other pulmonary physiologic impairments.
   - Manifestations of anxiety in patients with COPD include muscle tension, breathlessness, chronic worry, palpitations, feeling on edge, nausea, numbness, and fear of losing control.
   - Anxiety negatively correlates with quality of life in patients with COPD.

3. Between 6.5 and 43% of patients with COPD have a diagnosis of panic disorder.
   - Individuals with COPD and panic disorder have more frequent and longer respiratory hospital admissions than those without panic disorder, greater disability, and impaired function.
   - COPD self-management may be impaired in individuals with panic disorders.

4. The prevalence of cognitive dysfunction among individuals with COPD ranges from 10.4–48.5%.
   - Co-existing COPD and cognitive impairment is associated with increased respiratory-related and all cause hospitalizations and death.

5. The effect of COPD on social interactions has only recently been investigated.
   - Positively perceived social support is associated with fewer hospitalizations and COPD exacerbations, improved quality of life, and increased self-efficacy including participation in health promoting activities such as smoking cessation and physical activity.

References


COPD's Effects on Psychosocial Functioning and Familial Interactions


References


14 Management of Stable Chronic Obstructive Pulmonary Disease

Key Points:
1. Before initiating management, establish the diagnosis of chronic obstructive pulmonary disease (COPD):
   - respiratory symptoms: cough, phlegm production, and/or breathlessness
   - documented airflow limitation by spirometry or
   - radiographic evidence of emphysema
2. The most recent GOLD guidelines base management upon 3 factors:
   - severity of airflow limitation measured by FEV$_1$
   - respiratory healthcare visits in the prior 12 months
   - symptom score measured by the COPD Assessment Test or breathlessness measured by the modified Medical Research Council scale
3. In general, COPD pharmacologic management begins with a short acting bronchodilator and progresses with the addition of a long acting bronchodilator (either an anticholinergic or a long acting beta agonist), and lastly an inhaled corticosteroid.
4. Nonpharmacologic interventions such as oxygen, vaccinations, and pulmonary rehabilitation are essential components to comprehensive COPD management.

14.1 Management of Stable COPD

The prerequisite for the optimal management of COPD is the ascertainment of the correct diagnosis; COPD is diagnosed by respiratory symptoms (usually cough, sputum production, and/or dyspnea), the presence of airflow limitation (FEV$_1$/FVC < lower limit of normal), and the exclusion of other processes (see Chapter 3, COPD Recognition and Diagnosis: Approach to the Patient with Respiratory Symptoms).

The goals of COPD management are multiple and diverse: 1) reduce mortality, 2) preserve lung function, 3) decrease COPD-associated complications, 4) treat COPD-related comorbidities, 5) decrease the number and severity of COPD exacerbations, 6) relieve respiratory symptoms, especially breathlessness and cough, and 7) improve overall wellbeing. Although exacerbation prevention, reduction in healthcare utilization, and preservation of lung function are frequently the endpoints of investigations examining the effects of pharmacologic and nonpharmacologic interventions in COPD, relief of respiratory symptoms is often the principle goal when a primary care provider sees a patient with COPD.

The major symptoms experienced by patients with COPD are breathlessness, cough, and sputum production (Rennard, 2002; Leidy, 2003A). Assessment of these
symptoms should be performed at every healthcare encounter for individuals with COPD. Numerous surveys and assessment tools have been developed to assist clinicians with the evaluation of respiratory symptoms. One such tool is the Breathlessness, Cough, and Sputum Scale, a daily diary of COPD related symptoms that correlates with lung function measured by the FEV$_1$ and sputum volume (Leidy, 2003). This scale is simple and consists of only three questions: 1) How much difficulty did you have breathing today?, 2) How was your cough today?, and 3) How much trouble was your sputum today? Each question has 5 graded responses from none to severe (Leidy, 2003A; Leidy, 2003B). This questionnaire is limited to the three major respiratory symptoms associated with COPD. Numerous other disease-specific, as well as generic surveys, have been developed to assess quality of life in individuals with COPD. In a systemic review, the best instruments were the Chronic Respiratory Questionnaire (CRQ), COPD Assessment Test (CAT), Saint George Respiratory Questionnaire (SGRQ), and Living with COPD questionnaire (LCOPD) (Weldam, 2012). The CAT has been adopted in the most recent GOLD guidelines (Jones, 2009) (Figure 14.1).

14.1.1 Breathlessness

Breathlessness at rest and especially with exertion is a primary symptom of COPD. Dyspnea often limits action or patients avoid activities due to the fear of developing breathlessness. The cause of breathlessness in individuals with COPD is multifactorial with contributions from bronchospasm, desaturation, secretions, and cough but the major factor is dynamic lung hyperinflation. Lung hyperinflation is an increase in the volume of air remaining in the lungs at the end of exhalation that is associated with excessive loading and functional weakness of the respiratory muscles that precipitates mechanical dysfunction and sensory dysphoria (the sensation of breathlessness). Lung hyperinflation is caused by increased lung compliance and airflow limitation. In COPD, air is easily inhaled but exhalation is impeded by airflow limitation caused by increased resistance and reduced elastic recoil; if less air is exhaled than was inhaled, the lung begins to retain air, increasing the end expiratory lung volume (EELV). As EELV increases, the volume of air inhaled during subsequent breaths is decreased due to restriction of the inspiratory capacity, reducing the tidal volume, and impairing minute ventilation. Thus, the lungs are unable to meet ventilatory and oxygenation demands. The increase in respiratory rate that occurs with exertion further augments hyperinflation by reducing expiratory time causing more air trapping and elevation of EELV. As hyperinflation increases, the respiratory muscles are stretched or loaded causing discomfort; the stretching also causes functional weakness by putting the muscles at a mechanical disadvantage. The discomfort caused by stretching and loading of respiratory muscles by dynamic hyperinflation is a significant factor contributing to the sensation of breathlessness. Both pharmacologic and non-pharmacologic treatments may help to ameliorate dynamic hyperinflation.
Pursed lip breathing facilitates exhalation of air by creating an increased expiratory resistance that elevates the intra-airway pressure to maintain airway patency, reducing collapse due to diminished elastic recoil and increasing the amount of air expelled during exhalation. The improved expiratory airflow reduces air trapping and hyperinflation. Slow, deliberate, and controlled breathing utilizing pursed lip breathing helps to reduce the respiratory rate which increases the exhalation time that may also reduce air trapping and hyperinflation. Control of anxiety, relaxation techniques, and better awareness of the perception of breathlessness may also help reduce the rate of breathing. Oxygen and improved overall fitness from pulmonary rehabilitation or other conditioning programs may reduce ventilatory demand slowing the respira-
tory rate and increasing time in exhalation. Bronchodilators reduce airway resistance and permit improved lung emptying.

14.1.2 Cough

Chronic bronchitis is defined as cough and sputum production for at least 3 months of the year for two consecutive years. Individuals with mild to moderate airflow limitation report cough and sputum production more frequently than those with severe obstruction (von Hertzen, 2000). Causes of cough in COPD have not been well studied but inflammation, sputum clearance, and comorbidities such as bronchiectasis, gastroesophageal reflux disease, and postnasal drainage may all contribute. Early studies suggested that patients with COPD had a heightened cough response to capsaicin that was similar to individuals with asthma but further studies have been equivocal (Doherty, 2000).

Patients with COPD and chronic cough have longer durations of smoking, more impaired lung function, and are more likely to be current smokers (Kanner, 1999). The prevalence of chronic cough decreases by 80% 5 years after quitting smoking. Productive cough is a risk factor for the development of airflow limitation in nonsmokers and former smokers (Yamane, 2010).
Patients with moderately severe COPD and cough spend more time coughing during the day than at night (Smith, 2003). Cough frequency does not correlate with the severity of airflow limitation (Smith, 2003; Smith, 2004). Despite the frequent reporting of cough by patients with COPD, objective cough counts and time spent coughing, 12.3 s per hour during the day and 1.63 s per hour at night, are quite low (Smith, 2003; Smith, 2004).

Inhaled steroids do not affect cough frequency in patients with COPD (Doherty, 2000; Smith, 2004). Long acting beta agonists reduce cough more effectively than short acting beta agonists (Smith, 2004); in contrast, short acting anticholinergics reduce cough better than long acting anticholinergics (Smith, 2004). Codeine is not better than placebo in reducing cough frequency in patients with COPD (Smith, 2006).

14.1.3 Sputum Production

Airway mucus is usually a thin gel composed of water and mucins (glycosylated proteins) as well as components of the innate immune system: antimicrobial, immuno-modulatory, and protective proteins, that line the respiratory mucosal surface. Inhaled toxins and particles are trapped within the mucus and expelled from the lungs by ciliary beating and cough (Fahey, 2010). Cigarette smoke impairs cilia structure and function, induces mucin production, and reduces mucus hydration. Thus, more airway mucus remains in the lower airway and may become colonized with bacteria which can induce inflammation and inflammatory cell migration into the airway. Neutrophil-derived DNA increases the viscosity of the airway mucus further impairing clearance.

Patients with severe COPD frequently experience increased phlegm production and have more respiratory symptoms, less emphysema, and greater airflow limitation (Kim, 2011). Approximately 14% of individuals with airflow limitation have symptoms of chronic bronchitis and, compared with those with airflow limitation but no symptoms of chronic bronchitis, have worse lung function and overall health, more respiratory symptoms and exacerbations, greater limitations in physical activity, and an increased risk of mortality (Montes de Oca, 2012; Burgel, 2009; Kim, 2011). Most recently the COPDGene Study has shown that individuals with the chronic bronchitic phenotype of COPD have an accelerated rate of decline in lung function, increased risk of respiratory infections, more frequent nasal and respiratory symptoms, and increased frequency and severity of exacerbations (Kim, 2011).

Bronchiectasis is another contributing factor to cough and sputum production. Approximately 30–60% of individuals with COPD have chest CT evidence of bronchiectasis (Bafadhel, 2011; Martinez-Garcia, 2011). The presence of bronchiectasis is associated with increased frequency of bacterial colonization of the lower airway, more severe airflow limitation, and previous hospitalizations for COPD exacerbations.
Smoking cessation is associated with a reduction in phlegm production (Kanner, 1999). Airway clearance techniques such as postural drainage, percussion, vibration, and breathing exercises do not reduce COPD exacerbations, have variable effects on lung function, improve quality of life, and may promote short term increases in phlegm production (Osadnik, 2012). Mucolytics (such as N-acetyl cysteine) reduce exacerbation rates in patients with chronic bronchitis by approximately 20% (Poole, 2012).

14.2 Guidelines for the Management of COPD

There are multiple guidelines for the management of COPD that have been developed by numerous national and international health organizations. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) reports are the most widely disseminated international guidelines for the management of COPD and are continually updated (GOLD guidelines). Another source for practical advice for the management of COPD is the COPD Foundation Guide to COPD Diagnosis and Treatment (http://journal.copdfoundation.org/Portals/0/JCOPDF/Files/Issue1-Volume1/JCOPDF-2014-0124-Pocket-Guide.pdf).

COPD is a systemic inflammatory state with protean manifestations—COPD is not just a lung disease! (see Chapter 10. COPD Is a Multi-organ Disorder: Systemic Manifestations). Cardiovascular disease including coronary artery disease, stroke, and hypertension, osteoporosis, psychological disorders, especially anxiety and depression, skeletal muscle dysfunction, and lung cancer occur more frequently in individuals with COPD than in those with normal lung function even though they may have similar smoking histories. Treatment of COPD comorbidities should include optimal COPD management as well as appropriate management of the specific nonpulmonary process.

Most COPD treatment guidelines advocate an additive, incremental approach to the pharmacologic management of COPD. There has been poor adherence to most COPD guidelines and few studies have evaluated their effectiveness. At the Cincinnati VAMC, review of the prescribed respiratory medications and respiratory and nonrespiratory visits between 2000 and 2005 showed poor compliance with the GOLD pharmacologic treatment guidelines but correlation between respiratory treatments and the number of prior respiratory health care visits (Seaman, 2010). Another study from Switzerland showed that adherence to the GOLD guidelines did not affect respiratory symptoms, exacerbation rate, or lung function over 12 months (Jochmann, 2012). However, other studies have shown that better adherence with respiratory medications improves overall survival in individuals with COPD (Vestbo, 2009). Although these earlier guidelines classified disease impairment and based treatment recommendations upon the severity of airflow limitation (usually measured by the FEV₁), the most recent 2012 GOLD guidelines include an assessment of respiratory symptoms and prior healthcare encounters to assist in the determination of the optimal treatment regimen.
GOLD Guidelines for the Management of COPD

The GOLD guidelines recommend that each individual with COPD be evaluated to determine the severity of COPD, the effect of COPD on the individual’s overall health and well being, the risk of future COPD-related events (healthcare encounters or death), and COPD-related comorbidities (Figure 14.3). COPD severity is classified by the severity of airflow limitation measured by spirometry. The GOLD guidelines define airflow limitation as FEV<sub>1</sub>/FVC < 0.70 (see Chapter 4, Pulmonary Function Testing: Presence and Severity of Airflow Limitation/Obstruction).

The effects of COPD on an individual’s overall health and well being are evaluated by the COPD Assessment Test (CAT) (Figure 14.1) or the Modified British Medical Research Council (mMRC) breathlessness scale (Table 14.2).
Although there are numerous definitions of a COPD exacerbation (see Chapter 16, Management of Outpatient COPD Exacerbations and Chapter 17, Management of Inpatient COPD Exacerbations), the GOLD guidelines define a COPD exacerbation as an acute event characterized by worsening of the patient’s respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication (GOLD Guidelines). The best predictor of future exacerbations is a history of exacerbations in the prior year (Hurst, 2010). Severity of airflow limitation and use of systemic steroids are also associated with more frequent COPD exacerbations.

The GOLD multivariable COPD assessment is complex and requires several disparate pieces of data. It classifies patients as high or low risk based upon the severity of airflow limitation and history of exacerbations and then grades them as more or less symptomatic based upon their CAT or mMRC score (Figure 14.3). Patients with less symptoms, better spirometry, and fewer exacerbations are group A; patients with more symptoms, worse spirometry, and more frequent exacerbation are group D. Groups B and C are intermediate and have either more symptoms and lower risk or less symptoms and higher risk.
Pharmacologic Treatment of COPD

Medications for the treatment of COPD consist of short acting beta agonists (SABA), long acting beta agonists (LABA), short acting anticholinergics (SAch), long acting anticholinergics (LAch), inhaled (ICS) and enteral corticosteroids. Other medications include phosphodiesterase inhibitors, macrolide antibiotics (used for their anti-inflammatory not antibiotic effect), and mucolytics.

SABAs are usually the initial medication and should be used on an as needed rather than scheduled basis for patients in GOLD group A. (Figure 14.4) Combinations of SABA and SAch (such as Combivent®) should not be prescribed regularly because SABA’s should only be used on an as needed basis. If symptoms persist despite use of a SABA or if SABA use is excessive (greater than 3–4 times daily), an anticholinergic bronchodilator is usually added, GOLD Group B. LAch’s are usually preferred because of the ease of use and theoretical advantage of improved adherence with less fre-
quent dosing. A LABA may also be added. Combinations of a LABA and ICS or LABA and LACH may facilitate medication use and improve adherence, GOLD group C. ICS are recommended for patients with GOLD severe or very severe disease (FEV1<50%) and who have had two or more exacerbations in the prior year, GOLD Group D. ICS may also be beneficial in individuals who demonstrate bronchodilator responsiveness during spirometry testing (Chapter 9.4, COPD Phenotypes). Use of triple inhalers in COPD, LACH and LABA plus ICS, improves lung function and symptoms but does not reduce exacerbations compared with either treatment alone (Aaron, 2007).

Many patients with less severe and/or less COPD-related risk are prescribed ICS. It has been estimated that 70% of patients with COPD are treated with high-dose combination inhalers yet only 10% qualify under the current guidelines (Barnes, 2011). Similarly, significant over prescription of ICS compared with guidelines was noted among Veterans with COPD at the Cincinnati VAMC (Seaman, 2010). Use of ICS is associated with an increased risk of pneumonia in patients with COPD, OR 1.78 (95% CI, 1.50–2.12) (Kew, 2014).

Over the past 5 years, numerous new medications and novel medication combinations for the management of COPD have been approved by the US Food and Drug Administration (Table 14.3). The pharmacologic armamentarium for the treatment of COPD has doubled in the past several years and many new medications and combinations are in development.

### 14.3.1 Phosphodiesterase Inhibitors

Phosphodiesterases (PDEs) are a family of at least 11 isoenzymes that hydrolyze cAMP and cGMP. Inhibition of PDEs stimulates bronchodilation and also reduces pulmonary inflammation. Methylxanthines such as aminophylline or theophylline are non-specific PDE inhibitors that have been used for the treatment of asthma and COPD. These medications are limited by a narrow therapeutic serum drug range, frequent interaction with other medications, and poor tolerability. Most recently, specific inhibitors of PDE isoforms, especially PDE4, have been developed and shown to be effective in the management of COPD. Roflumilast was approved by the FDA in 2011 as adjuvant treatment to reduce COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations (Reid, 2012).

### 14.3.2 Macrolides

Macrolides such as erythromycin and azithromycin have anti-inflammatory properties in addition to anti-microbial effects. Recent studies have shown that either daily erythromycin or azithromycin decrease the frequency of COPD exacerbations in patients with a history of exacerbations. (Martinez, 2008; Seemungal, 2008; Albert,
Although it remains unclear which subgroup of patients with COPD will benefit best from macrolide treatment and whether dosing should be daily or thrice weekly, current recommendations are to consider daily macrolide treatment in patients who, despite maximal standard bronchodilator therapy, have at least 2 exacerbations yearly (Mammen, 2012). Potential adverse effects of prolonged macrolide use include development of bacterial resistance, cardiovascular events, and hearing loss.

**Table 14.3: Federal Drug Administration Approved Medications for COPD**

<table>
<thead>
<tr>
<th>Class</th>
<th>Generic Name</th>
<th>Brand Name</th>
<th>FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>SABA</td>
<td>Albuterol</td>
<td>Ventolin HFA</td>
<td>2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Proventil HFA</td>
<td>1999</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Xopenex</td>
<td>2002</td>
</tr>
<tr>
<td>SACH</td>
<td>Ipratropium</td>
<td>Atrovent HFA</td>
<td>2004</td>
</tr>
<tr>
<td>SABA + SACH</td>
<td>albuterol + ipratropium</td>
<td>Duoneb</td>
<td>2001</td>
</tr>
<tr>
<td>LACH</td>
<td>Tiotropium bromide</td>
<td>Spiriva HandiHaler</td>
<td>2004</td>
</tr>
<tr>
<td></td>
<td>Umeclidinium</td>
<td>Incruse Ellipta</td>
<td>2014</td>
</tr>
<tr>
<td></td>
<td>Aclidinium bromide</td>
<td>Tudorza Pressair</td>
<td>2012</td>
</tr>
<tr>
<td>LABA</td>
<td>Formoterol fumarate</td>
<td>Foradil Aerolizer</td>
<td>2001</td>
</tr>
<tr>
<td></td>
<td>Salmeterol</td>
<td>Serevent Diskus</td>
<td>1998</td>
</tr>
<tr>
<td></td>
<td>Indacaterol maleate</td>
<td>Arcapta</td>
<td>2011</td>
</tr>
<tr>
<td></td>
<td>Arformoterol tartrate</td>
<td>Brovana</td>
<td>2006</td>
</tr>
<tr>
<td></td>
<td>Olodaterol</td>
<td>Stiverdi Respimat</td>
<td>2014</td>
</tr>
<tr>
<td>LABA + ICS</td>
<td>Formoterol + Budesonide</td>
<td>Symbicort</td>
<td>2009</td>
</tr>
<tr>
<td></td>
<td>Salmeterol + Fluticasone furoate</td>
<td>Advair Diskus</td>
<td>2003</td>
</tr>
<tr>
<td></td>
<td>Vilanterol + Fluticasone furoate</td>
<td>Breo Ellipta</td>
<td>2013</td>
</tr>
<tr>
<td>LACH + LABA</td>
<td>Umeclidinium+ vilanterol</td>
<td>Anoro Ellipta</td>
<td>2013</td>
</tr>
<tr>
<td>PDE 4 Inhibitor</td>
<td>Roflumilast</td>
<td>Daliresp</td>
<td>2011</td>
</tr>
</tbody>
</table>

Abbreviations: SABA: short acting bronchodilator; SACH: short acting anticholinergic; LACH: long acting anticholinergic; LABA: long acting bronchodilator; ICS: inhaled corticosteroid; PDE: phosphodiesterase
14.3.3 Mucolytics

Mucolytics such as n-acetylcysteine and carbocysteine may reduce COPD exacerbations and improve health related quality of life in patients with COPD (Decramer, 2010). In one prospective study, n-acetylcysteine reduced hyperinflation (Stav, 2009).

14.3.4 Supplemental Oxygen

Supplemental oxygen improves survival in patients with hypoxemia at rest ($\text{PaO}_2 < 55$ torr or $\text{SpO}_2 < 88\%$; or $\text{PaO}_2 < 60$ and $>55$ torr with evidence of cor pulmonale). The mechanism(s) by which supplemental oxygen improves mortality is not known. Oxygenation should be measured on room air at rest, with exertion, and during sleep after the administration of supplemental oxygen to insure that desaturation is prevented. Although Medicare and most insurances reimburse for supplemental oxygen during exercise or at night with evidence of exercise or nocturnal desaturation, there is no substantive evidence that supplemental oxygen during exercise or at night is beneficial in individuals with stable COPD and normoxemia at rest.

14.4 Nonpharmacologic Treatment of COPD

Smoking cessation is the singularly most important intervention for the prevention and treatment of COPD. Please see Chapter 7, Smoking Cessation, for further discussion of smoking cessation.

Both influenza and pneumococcal vaccination are recommended for individuals with COPD. Influenza vaccination reduces mortality, outpatient visits, hospitalizations, and exacerbations caused by influenza (Varkey, 2009). In contrast, although pneumococcal vaccination reduces the incidence of invasive pneumococcal disease, it has not shown any significant effect on mortality, rates of pneumonia or exacerbations, lung function, or cost effectiveness (Varkey, 2009; Walters, 2010). Vaccination against both influenza and pneumococcus may reduce COPD exacerbations more effectively than either vaccine alone (Varkey, 2009).

Pulmonary rehabilitation is a multidisciplinary program of education and exercise that teaches patients with COPD about their disease, its treatment, and mechanisms to cope with its consequences as well as an exercise and conditioning program. Pulmonary rehabilitation has the best effect when it is integrated into a comprehensive COPD management program that encourages behavior change and a shift from provider initiated to patient initiated care. Patients with COPD who maintain physical activity have less breathlessness with exertion, better health related quality of life, improved long term function and independence, and better psychological and physiological function.
Physical inactivity is associated with worse survival, increased risk of respiratory-related hospitalization, lower self-reported health status, and greater systemic inflammation (Watz, 2014). Pulmonary rehabilitation improves respiratory symptoms (Lacasse, 2006). In addition to improving respiratory symptoms, pulmonary rehabilitation decreases health care utilization and may improve survival (Ries, 2008). Home based PR programs have the equivalent benefit of hospital based programs (Bourbeau, 2010).

**Lung volume reduction** either surgical or endoscopic via endobronchial valve placement may also be effective in certain patients with COPD. Surgical lung volume reduction improves exercise tolerance, quality of life, and survival in selected patients with COPD (Tidwell, 2012). LVRS is only beneficial in patients with upper lobe emphysema and poor exercise tolerance and is detrimental in individuals with $\text{FEV}_1 < 20\%$.

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**Table 14.4: Medicare Oxygen Reimbursement Guidelines**

<table>
<thead>
<tr>
<th>Condition</th>
<th>$\text{PaO}_2$</th>
<th>$\text{SpO}_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Awake, at rest</td>
<td>$&lt; 55$ mm Hg and $66–59$ mm Hg and dependent edema or</td>
<td>$&lt; 88%$ and $= 89%$ and dependent edema or</td>
</tr>
<tr>
<td></td>
<td>cor pulmonale and pulmonary hypertension by right heart</td>
<td>cor pulmonale and pulmonary hypertension by right heart</td>
</tr>
<tr>
<td></td>
<td>catheterization or ECHO or</td>
<td>catheterization or ECHO or</td>
</tr>
<tr>
<td></td>
<td>$P$ pulmonale on ECG (P wave $&gt; 3$ mm in leads II, III, or AVF) or</td>
<td>$P$ pulmonale on ECG (P wave $&gt; 3$ mm in leads II, III, or AVF) or</td>
</tr>
<tr>
<td></td>
<td>erythrocythemia (HCT $&gt; 56%$)</td>
<td>erythrocythemia (HCT $&gt; 56%$)</td>
</tr>
<tr>
<td>Exercise</td>
<td>$&lt; 55$ mm Hg and documentation that use of supplemental</td>
<td>$&lt; 88%$ mm Hg and documentation that use of supplemental</td>
</tr>
<tr>
<td></td>
<td>oxygen ameliorates the decline in oxygen levels</td>
<td>oxygen ameliorates the decline in oxygen levels</td>
</tr>
<tr>
<td></td>
<td>(Duration of desaturation and type/level of exertion are not specified.)</td>
<td>(Duration of desaturation and type/level of exertion are not specified.)</td>
</tr>
<tr>
<td>Sleep</td>
<td>$&lt; 55$ mm Hg or $\text{PaO}_2$ declines $&gt; 10$ mm Hg from awake, resting level and dependent edema or cor pulmonale or pulmonary hypertension by right heart catheterization or ECHO or $P$ pulmonale on ECG (P wave $&gt; 3$ mm in leads II, III, or AVF) or erythrocythemia (HCT $&gt; 56%$) (Duration of desaturation and type/level of exertion are not specified.)</td>
<td>$&lt; 88%$ or $\text{SpO}_2$ declines $&gt; 5%$ from awake, resting level and dependent edema or cor pulmonale or pulmonary hypertension by right heart catheterization or ECHO or $P$ pulmonale on ECG (P wave $&gt; 3$ mm in leads II, III, or AVF) or erythrocythemia (HCT $&gt; 56%$) (Duration of desaturation and type/level of exertion are not specified.)</td>
</tr>
</tbody>
</table>
of predicted, DLCO < 20% of predicted, or diffusely distributed emphysema. Patients who are being considered for LVRS should be referred for pulmonary consultation. Endoscopic LVRS is a newer technique that may also be beneficial in select patients.

14.5 Management of COPD-related Nonpulmonary Co-morbidities

Because COPD is a multisystemic disorder with protean nonpulmonary manifestations, it is essential to evaluate and treat patients with COPD for conditions such as anemia, diabetes, lung cancer, and cardiovascular disease. (Reviewed in Chapter 10, COPD Is a Multi-Organ Disorder: Systemic Manifestations.)

14.6 Summary Points

1. Establish a definitive diagnosis of COPD before initiating treatment.
2. The principal symptoms of COPD are breathlessness, cough, and sputum production.
3. There are several well validated instruments (such as the COPD Activity Test) to assess and monitor serially COPD’s effects on quality of life and respiratory symptoms.
4. Pharmacologic treatment for COPD begins with an as needed short acting bronchodilator, usually a SABA. The subsequent medication is a long acting bronchodilator, either LACH or LABA. Next, the other class of long acting bronchodilator is added and inhaled corticosteroids are usually the final inhaler category. (Individuals with COPD who have a response to bronchodilators may be more responsive to inhaled corticosteroids.)
5. Recent definitions of new COPD phenotypes will help to individualize COPD treatment regimens.
6. Dynamic hyperinflation is the major cause of exertional dyspnea and responds to pursed lip breathing and a slowing of the respiratory rate.
7. Nonpharmacologic treatments that are effective in the management of COPD include supplemental oxygen, lung volume reduction surgery, pulmonary rehabilitation and vaccinations, especially influenza.

References


15 Practical Guide to Correct Inhaler Use

Key Points
1. Knowledge of proper inhaler techniques enables providers to educate patients with COPD how to use their medications correctly and achieve maximal benefits.
2. Correct inhaler use is critical to obtaining maximal therapeutic benefit.
3. Repetitive inhaler education and direct observation play crucial roles in ensuring that patients use their inhalers correctly.
4. Correct use of pressurized metered-dose inhalers (pMDIs) requires coordination between activating the canister and slowly inhaling the aerosol.
5. Using a spacer with a pMDI improves effective drug delivery to the lungs.
6. Multidose dry powder inhalers (DPIs) are inhalation-triggered by the patient and do not require activation-inhalation coordination for proper use.
7. The Respimat® Soft Mist Inhaler® (SMI) provides the same level of bronchodilation as pMDIs without spacers and DPIs, but at roughly half the dose of medication. The Respimat® SMI has been shown to have greater lung and less oropharyngeal deposition of medication compared to pMDIs without spacers and DPIs.
8. Nebulizers are an alternative to short acting bronchodilator pMDIs when patients are unable to use a pMDI properly or when they are hospitalized. There is not a significant clinical therapeutic difference between medications delivered by pMDI with a spacer and by nebulizer.

15.1 Introduction

Inhaled medications have a critical role in the treatment of chronic obstructive pulmonary disease (COPD). The goals of treatment include bronchodilation, minimizing airway inflammation, preventing exacerbations, improving quality of life (QOL), and decreasing mortality (Celli, 2004). The success and potential benefits of treatment depend upon successfully delivering the drug to the appropriate location in the lungs. Inhalers, when properly used, serve to target the drug directly to the lungs (Dolovich, 2005; Ernst, 1998; Pauwels, 1997). Inhaled medications are a preferred treatment for COPD, as compared to oral or intravenous (IV) medications, because they can be distributed to the lungs as an aerosol in smaller quantities, leading to significantly fewer systemic side effects (Aerosol Consensus Statement, 1991; GOLD website).

The ability of the drug to reach the smaller, more peripheral airways of the lung is critical for inhaler efficacy. Inhaled particles that are traveling at high velocity or are too large tend to be delivered to the larger (more proximal) airways, thus not reaching their target. To reach the smaller airways, particles must be moving slowly enough
Practical Guide to Correct Inhaler Use

and must be small enough (1–5µm) to navigate the multiple directional bifurcations within the distal airways (Burton, 1992; Dolovich, 1991).

There are a variety of available inhalational devices that deliver medication in an aerosol form. The choice of medication, as well as the ability of the patient, ultimately determines what type of inhaler to prescribe (Broeders, 2009; Hanania, 1994; Vincken, 2010) (Table 15.1). In this chapter, we will review most commonly prescribed inhalers (pressurized metered-dose inhalers [pMDIs], multidose dry powder inhalers [DPIs], Respimat® inhaler, and nebulizers), how they work, and the correct steps to use them properly.

### 15.2 Inhaler Education and Errors in Inhaler Technique

The most commonly used inhalation devices are pMDIs, DPIs, Respimat® and nebulizers. (Table 15.2) If used properly, each of these devices can deliver a precise amount of drug in small particles that can reach the terminal airways and produce a bronchodilating effect. Incorrect inhaler use by patients decreases medication adherence and diminishes the therapeutic benefit (Crompton, 1982; McFadden, 1995). Errors in inhaler technique occur in as many as 90% of patients with COPD (Crompton, 1982; Crompton, 2006; Fink, 2005; Lavorini, 2008; McFadden, 1995; Rees, 2005; Wieshammer, 2008). Factors associated with improper inhaler use in patients with COPD include age, impaired cognitive function, and poor training of healthcare professionals responsible for teaching correct inhaler use (Leiva-Fernández, 2012). Problems are further increased when patients use multiple inhalation delivery devices, often
confusing the different techniques required for each unique device (van der Palen, 1999).

Errors in inhaler technique are often a consequence of inadequate or poor education. Inhaler education prior to initiation of inhalation therapy is critical and written instruction alone are inadequate. Verbal instruction, assessing correct inhaler technique, and reassessment decrease inhaler misuse (De Boeck, 1999; Leiva-Fernández, 2012). Patients who have recurrent inhaler education have better inhaler techniques compared with those who only receive instruction at the time of prescription (Gracia-Antequera, 1999). The Global Initiative for Chronic Obstructive Lung Disease (GOLD) and the National Institute for Health and Care Excellence (NICE) both recommend inhaler education and device training when a patient is prescribed a new inhaler (GOLD, NICE websites). They also recommend that correct inhaler technique be assessed at each patient encounter. However, up to 25% of patients do not receive any verbal instruction when prescribed an inhalational device (Lavorini, 2008).

There are several modalities used to provide inhaler education and improve correct use. Demonstration of inhaler use by healthcare professionals is effective at both teaching and assessing the correct use of inhaler devices (Bosnic-Anticevich, 2010; Nimmo, 1993). However, healthcare professionals often do not know how to

---

**Table 15.2: Medications commonly used for the treatment of COPD**

<table>
<thead>
<tr>
<th>Pressurized Metered-Dose Inhalers (pMDIs) (Can use with a spacer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albuterol</td>
</tr>
<tr>
<td>Ipratropium</td>
</tr>
<tr>
<td>Albuterol / Ipratropium</td>
</tr>
<tr>
<td>Budesonide / Formoterol</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Multidose Dry Powder Inhalers (DPIs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formoterol</td>
</tr>
<tr>
<td>Mometasone</td>
</tr>
<tr>
<td>Budesonide</td>
</tr>
<tr>
<td>Tiotropium</td>
</tr>
<tr>
<td>Fluticasone / Salmeterol</td>
</tr>
<tr>
<td>Aclidinium</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Respimat® Soft Mist Inhaler (SMI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipratropium</td>
</tr>
<tr>
<td>Tiotropium</td>
</tr>
<tr>
<td>Albuterol / Ipratropium</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nebulized Solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albuterol</td>
</tr>
<tr>
<td>Ipratropium</td>
</tr>
<tr>
<td>Albuterol / Ipratropium</td>
</tr>
</tbody>
</table>
Practical Guide to Correct Inhaler Use

use the inhalation device and often cannot use it correctly themselves (Guidry, 1992; Hanania, 1994; Keston, 1993). Coaching has also been used to improve the ability to use inhalers; however, many patients often quickly revert back to an incorrect inhalation technique (Crompton, 1982; Duerden, 2002). For the patient to have the optimum benefit of their inhaled medication, it is of the utmost importance that the healthcare professional educating the patient has proper knowledge of the inhaler, knows what inhalers are appropriate for individual patients, and can teach correct inhaler use.

15.3 Inhalation Delivery Systems

15.3.1 Pressurized Metered-Dose Inhalers (pMDIs)

The pMDI has long been the most commonly used inhaled device because it is small, portable, inexpensive, and relatively easy to use (Vincken, 2010). Benefits of pMDIs are that they are pocket-sized, efficient, and can deliver many doses of medication quickly with precision. The pMDI is a pressurized canister filled with liquid medication placed in a chamber with a mouthpiece. Built into this system is a metering valve that delivers a specific quantity of the drug with each use. The wet aerosol is delivered to the lungs by a propellant. Historically, chlorofluorocarbon (CFC) was used as a propellant but CFC use is banned by the Montreal Protocol on Substances that Deplete the Ozone Layer because CFCs have been linked to depletion of the ozone layer in the upper atmosphere. CFCs have since been replaced by hydrofluoroalkanes (HFA), which are more environmentally friendly (Dolovich, 1999). The newer pMDIs formulated with HFAs have, in part, many of the same inhaler characteristics (smaller...
Inhalation Delivery Systems

Particle sized and less need for actuation-inhalation coordination) as the CFC inhalers (Leach, 1998; Melani, 2007).

pMDIs are designed to deliver an exact dose of medication to the lungs (Wilson, 1993). When the patient presses the canister, a one-way metering valve opens. The drug is aerosolized and the patient inhales it from the mouthpiece. The particle sizes within the aerosol vary, and the larger particles are deposited more proximally and the smaller particles dispersed to the smaller airways (Finlay, 2001; Hickey, 2004; Swarbrick, 2007). (Figure 15.1) For pMDIs to deliver the medication to the lungs properly, there must be coordination between canister activation and aerosol inhalation (Crompton, 1982; Larsen, 1994). pMDIs are both a reliable and effective inhaler device when used correctly. The coordinated steps that must be taken to use the pMDI correctly are shown in Table 15.3.

Determining the amount of medication remaining in the pMDI canister has been difficult to assess. The float method was used in the past to determine the amount of medication remaining in pMDIs. In the float method, the canister containing medication was placed in water. If the canister was empty it would float. How full the canister was full of medication would determine how far it would sink. Float testing is highly variable, product-specific, and a function of canister size, design, content, and method of testing (Brock, 2002). Float testing is not recommended as an appropriate method to measure medication adherence. Directly weighing the canister and dose counters are the most accurate ways to assess the medication remaining in the

Table 15.3: Correct steps for using pMDI without a spacer

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Shake the inhaler well immediately before each use.</td>
</tr>
<tr>
<td>2.</td>
<td>Remove cap from mouthpiece</td>
</tr>
<tr>
<td>3.</td>
<td>Check mouthpiece for foreign objects.</td>
</tr>
<tr>
<td>4.</td>
<td>Make sure the canister is fully inserted into the actuator.</td>
</tr>
<tr>
<td>5.</td>
<td>Prime inhaler if using for the first time or if the inhaler has not been used for over 2 weeks. Do this by spraying the inhaler 2–3 times away from the face.</td>
</tr>
<tr>
<td>6.</td>
<td>Breathe out gently and fully through the mouth, trying to remove as much air from the lungs as possible.</td>
</tr>
<tr>
<td>7.</td>
<td>Open the mouth wide, and place the open end of the mouthpiece about 1–2 inches from the mouth and inhale (slowly and deeply; as if sipping hot soup). Press canister down into the mouthpiece to actuate the aerosol at the beginning of inhalation while continuing to inhale deeply.</td>
</tr>
<tr>
<td>8.</td>
<td>At end of inspiration, hold breath for 10 seconds, or as long as possible, then breathe out slowly.</td>
</tr>
<tr>
<td>9.</td>
<td>If more puffs are needed (albuterol and ipratropium), wait for a few seconds before repeating steps 4–8.</td>
</tr>
</tbody>
</table>
pMDI canister. Dose counters have now been added to some pMDIs brands over the past decade. These devices display the number of doses/actuations that remain in the inhaler. The accuracy of dose counters depends upon the ability of the dose counter to decrease by one unit each time the patient actuates the inhaler. The dose counter should also be ergonomic (patient-friendly), and sustainable (lasting for the lifetime of the inhaler) (Weinstein, 2011).

### 15.3.2 Spacer Utilization

pMDIs are good inhalational devices for patients with COPD, but medication effectiveness using this type of inhaler is limited by the coordination of multiple steps, fine motor control, hand / finger strength, arthritis or other hand deformity, and, most importantly, precise hand-breath coordination. One way to minimize the issue of hand-breath coordination with a pMDI is to use a spacer. These devices improve drug delivery to the patient who is either non cooperative with pMDI use without the spacer, or unable to master correct pMDI usage. Spacers improve effective drug delivery when using the pMDI (Brennan, 2005; Melani, 2004). A spacer consists of a holding chamber with a one-way valve that connects to the mouthpiece of the pMDI. After activation of the pMDI, the medication aerosol is contained within the holding chamber and slowly inhaled by the patient. The one-way valve opens during inspiration and closes during expiration. This valve helps prevent drug loss which commonly occurs when patients cannot coordinate activating the canister and inhaling the aerosol (Dolovich, 1983). The spacer can also help to deliver the medication effectively to the smaller, more peripheral airways by slowing down the smaller particles and holding them in suspension for about one second, allowing some of the propel-lant surrounding the drug to evaporate. (Figure 15.2) Larger drug particles are also retained or deposited within the spacer during inhalation, thus limiting the inhaled aerosol to small particles that can reach the terminal airways (Ahrens, 1995; Barry, 1996). Another benefit is that larger particles will not reach the oropharynx, decreasing potential side effects. Spacers decrease oropharyngeal candidiasis associated with inhaled corticosteroid use; however, they do not decrease the rate of dyspho-
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Despite the benefits of spacer use, they are infrequently prescribed or used. This reduced adherence may be due to the size of the spacer (they are long, bulky, and not conveniently transported), and patients are often embarrassed to use them in public. Another disadvantage of the spacer is that it requires frequent cleaning by a standard procedure (Bisgaard, 2007; Van der Palen, 1999). (Table 15.4)

### 15.3.3 Multidose Dry Powder Inhalers (DPIs)

DPIs were developed as alternative inhalers for patients who have difficulty using pMDIs and as environmentally friendly alternatives to CFC containing pMDI. DPIs specifically address issues with actuation-inhalation synchronization as well as potential allergic reactions to the propellants in the pMDIs (Beaucage, 2002). They resolve actuation-inhalation difficulties by being inhalation-triggered. They deliver medication, in the form of a dry powder, to the smaller airways. The medication is released in the form of small particles that are inhaled into the airways when the patient takes a breath. The factors that determine the amount of medication delivered by DPIs are the inspiratory volume and flow produced by the patient. There are a variety of DPIs, and
Figure 15.3: Aerolizer® multidose dry powder inhaler (DPI)

Figure 15.4: Handihaler® multidose dry powder inhaler (DPI)

Figure 15.5: Twisthaler® multidose dry powder inhaler (DPI)
with each one the amount of inspiratory flow needed to deliver the medication to the correct location varies. Examples of DPIs include the Twisthaler®, Handihaler®, and Aerolizer®. (Figures 15.3–15.5) The correct steps for commonly used DPIs are shown in Tables 15.5–15.7.

The main advantages of DPIs include: they do not requiring a propellant for aerosolization and are ecologically friendly; they are breath-triggered and do not require the precise hand-inhalation coordination of pMDIs (Melani, 2007; Virchow, 2008).

Table 15.5: Correct steps for Using Formoterol (Foradil Aerolizer®) DPI

<table>
<thead>
<tr>
<th>Step</th>
<th>Instruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Hold the base of the inhaler firmly and twist the mouthpiece in the direction of the arrow to open.</td>
</tr>
<tr>
<td>2.</td>
<td>Push the buttons in on each side to make sure that you can see 4 pins in the capsule-chamber of the inhaler.</td>
</tr>
<tr>
<td>3.</td>
<td>Remove one capsule from the blister packer by peeling off the paper backing that covers one capsule, and pushing the capsule through the foil.</td>
</tr>
<tr>
<td>4.</td>
<td>Place the capsule in the capsule-chamber in the base of the inhaler and twist the mouthpiece back to the closed position.</td>
</tr>
<tr>
<td>5.</td>
<td>Hold the mouthpiece of the inhaler upright and press both buttons at the same time. Only press the buttons ONCE. There will be a click as the capsule is being pierced.</td>
</tr>
<tr>
<td>6.</td>
<td>Release the buttons.</td>
</tr>
<tr>
<td>7.</td>
<td>Keep the inhaler level, with the blue buttons to the left and right (not up and down).</td>
</tr>
<tr>
<td>8.</td>
<td>Breathe out and exhale fully.</td>
</tr>
<tr>
<td>9.</td>
<td>Place the mouthpiece in mouth and close lips around it.</td>
</tr>
<tr>
<td>10.</td>
<td>Breathe in quickly and deeply. This will cause the capsule to spin around in the chamber and deliver the dose of medicine. There will be a whirring noise and a sweet taste due to the sugar filler in the capsule.</td>
</tr>
<tr>
<td>11.</td>
<td>Remove the inhaler from mouth and continue to hold breath as long as possible, and then exhale.</td>
</tr>
<tr>
<td>12.</td>
<td>Open the inhaler to see if any powder is still in the capsule. If any powder remains in the capsule repeat steps 8 to 11. Most people are able to empty the capsule in one or two inhalations.</td>
</tr>
<tr>
<td>13.</td>
<td>After use, open the inhaler, remove and discard the empty capsule. Do not leave a used capsule in the chamber.</td>
</tr>
<tr>
<td>14.</td>
<td>Close the mouthpiece and replace the cover.</td>
</tr>
</tbody>
</table>

Table 15.6: Correct steps for using Tiotropium (Spiriva Handihaler®) DPI

<table>
<thead>
<tr>
<th>Step</th>
<th>Instruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>15.</td>
<td>Open Handihaler by lifting the cap and the mouthpiece on the top to reveal capsule insertion site.</td>
</tr>
<tr>
<td>16.</td>
<td>Separate one of the blisters from the blister card, open, and remove the capsule.</td>
</tr>
<tr>
<td>17.</td>
<td>Insert the capsule and close the mouthpiece firmly against the gray base until it clicks shut.</td>
</tr>
<tr>
<td>18.</td>
<td>Press the green piercing button once until it is flat (flush) against the base, then release.</td>
</tr>
<tr>
<td>20.</td>
<td>Place Handihaler mouthpiece in mouth and breathe in deeply until lungs are full. The capsule will vibrate (rattle).</td>
</tr>
<tr>
<td>21.</td>
<td>To take a full daily dose, inhale twice from the same capsule by repeating steps 5 and 6.</td>
</tr>
</tbody>
</table>
Disadvantages of DPIs include: inability to use them with non-cooperative patients or those being ventilated via endotracheal tube or tracheotomy tube; cannot use a spacer to improve effective drug delivery; the amount of drug delivered is not as accurate, or reproducible, compared to pMDIs; patients who cannot generate appropriate inspiratory volume or flow will receive inadequate drug doses; each individual DPI has its own steps for correct use requiring dexterity and understanding of each inhaler (Clark, 1993; Fuller, 1995; Olsson, 1998; Robbins, 2005; Tarsin, 2006).

15.3.4 Respimat® Soft Mist Inhaler® (SMI®)

The Respimat® SMI® is the most recent inhaler delivery system to be developed as an alternative to pMDIs. The Respimat® SMI® forces a solution carrying the medication through a series of channels with two nozzles on the end. These nozzles focus two fluid jets at a convergence, producing a vapor of medication-containing droplets of a precise size that can be inhaled (Dalby, 2004; Dalby, 2011; Panos, 2013). (Figure 15.6) This inhaler was also developed to deliver the vapor at a slower velocity, thus increasing the window of time for successful inhalation, decreasing drug deposition in the oropharynx, and increasing the amount of medication successfully reaching the lungs. A number of studies have confirmed less oropharyngeal and greater lung deposition with the Respimat® SMI® compared to pMDIs without spacers and DPIs (Brand, 2008; Khachikian, 2012; Newman, 1996; Newman, 1998; Pitcaim, 2005). Another benefit of the Respimat® SMI® is that it provides the same level of bronchodilation that pMDIs offer at a much lower dose (Iacono, 2000; Kilfeather, 2004; Ram, 2011; Zuwallack, 2010).

To use the Respimat® SMI®, a medication-containing cartridge must be inserted into the delivery system. This device is activated by twisting the base 180° (half a turn) until it clicks. This twisting loads the fluid into the dosing chamber. The patient then

---

Table 15.7: Correct steps for using Mometasone (Asmanex Twisthaler®) DPI

<table>
<thead>
<tr>
<th>Step</th>
<th>Instruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Hold the inhaler upright, with the colored portion on the bottom.</td>
</tr>
<tr>
<td>2.</td>
<td>Remove the cap of the inhaler while it is in this upright position. Holding the colored base, twist the cap in a counterclockwise direction to remove it. Removing the cap loads the inhaler with the medicine.</td>
</tr>
<tr>
<td>3.</td>
<td>Breathe out fully.</td>
</tr>
<tr>
<td>4.</td>
<td>Insert inhaler in mouth, holding it in a horizontal (on its side) position.</td>
</tr>
<tr>
<td>5.</td>
<td>Firmly close lips around the mouthpiece and take in a fast, deep breath. Do not cover the ventilation holes while inhaling the dose.</td>
</tr>
<tr>
<td>6.</td>
<td>Remove the inhaler from mouth and hold breath for about 10 seconds.</td>
</tr>
<tr>
<td>7.</td>
<td>Wipe mouthpiece dry, if needed, place cap back on mouthpiece, and firmly close the inhaler. A “click” will signify the cap is fully closed. This is the only way to be sure that the next dose is loaded the right way.</td>
</tr>
</tbody>
</table>
presses the dose-release button sending the fluid through the series of channels with nozzles at the end producing an inhalable particle vapor that exits the device. The coordinated steps that must be taken to use the Respimat® SMI® correctly are shown in Table 15.8.

15.3.5 Nebulized Solutions

Prior to the development of pMDIs and DPIs, inhaled medications were delivered via nebulizer. They transform the liquid form of medication into an aerosol of particles of various sizes that can be inhaled by mouthpiece or mask. The medication is inhaled while the patient is tidal breathing and does not require a deep, coordinated inspiration. To use a nebulized solution, one must have a nebulizer, air or oxygen compressor, and a mask or mouthpiece. (Figure 15.7) (Table 15.9) The types of medication delivered via nebulizer vary (steroids, short acting bronchodilators, and long acting
Table 15.8: Correct steps for using Respimat® SMI®

1. Remove cartridge from box and push the narrow end of the cartridge into the inhaler. The cartridge will not sit flush with the inhaler, with 1/8 of an inch of the cartridge sticking out of the inhaler.
2. Place clear base over the top of the cartridge.

To Prime
1. Prime inhaler if using for the first time, or if it has not been used in 3 weeks.
2. To prime, hold the inhaler upright, with the orange cap closed. Turn the clear base in the direction of the white arrows on the label until it clicks (half a turn). Flip the orange cap until it snaps fully open. Point inhaler toward the ground and press the dose release button. Repeat three more times.

To Use
1. Hold the inhaler upright with the orange cap closed, so it does not accidentally discharge a dose of medicine.
2. Turn the clear base in the direction of the white arrows on the label until it clicks (half a turn / 180°).
3. Flip the orange cap until it snaps fully open.
4. Breathe out slowly and fully, and then close lips around the end of the mouthpiece without covering the air vents.
5. Point inhaler to the back of throat.
6. While taking in a slow, deep breath by mouth, press the dose release button and continue to breathe in slowly for as long as possible.
7. Hold breath for 10 seconds or for as long as comfortable.

bronchodilators), and their delivery will depend on the drug’s solubility and if they are in a solution or a suspension.

The ability of a nebulizer to deliver medications to the lungs successfully depends upon many factors, especially the patient’s breathing pattern and the nebulizer output. As the drug is nebulized, its concentration in solution increases, leaving up to 50% of the drug in the reservoir (Johnson, 1989). The flow of gas in the nebulizer can alter the amount of drug delivered by changing particle size and nebulizer time. A flow rate between 6 and 10L/min can deliver approximately 2.5 mL of drug solution over 5–10 minutes (Muers, 1997). The patient should have a tidal (slow and regular) breathing pattern while inhaling the aerosol. It is also important to note these medications should be inhaled by breathing in and out through the mouth. Nebulizers are widely popular, often used, and are thought to be the most effective way to deliver inhaled medication. This, however, is not the case as only about 5% of the nebulized medication makes it to the smaller airways (Johnson, 1989). The rest of the medication is either delivered proximally, exhaled, or lost in the form of condensation in the reservoir, tubing, mouthpiece, or on the face.

There are a number of disadvantages to using a nebulizer. The process of delivering an inhaled medication to the lungs is long, inconvenient, and cumbersome (Melani, 2007). It is almost impossible to precisely deliver a set dose of medication with a nebulizer (Johnson, 1989). Nebulizers need to be cleaned frequently to prevent
Inhalation Delivery Systems

Contamination of the nebulized aerosols. Contamination has occurred frequently with the following microorganisms: methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*, *Burkholderia* species, and *Stenonotrophomonas* species (Berlinski, 2006; Melani, 2001). Most nebulizers are not portable.

There have been many studies comparing pMDIs (with a spacer) to nebulizers, showing that both are equally effective. Some studies favor pMDI use with a spacer over nebulizers in acute care and hospital settings, citing similar efficacy and potential cost savings (Comargo, 2000; Idris, 1993). The GOLD guidelines do not recommend the use of nebulizers for regular maintenance therapy in the treatment of COPD (GOLD website). The American Thoracic Society (ATS) and the European Respiratory Society (ERS) guidelines suggest that nebulizers can be used in the following situations for COPD: when using short acting bronchodilators; when patients cannot use an inhaler properly; and when patients are hospitalized (easier to deliver by respiratory therapist and requires little patient effort) (Celli, 2004).

### Table 15.9: Correct steps for using nebulizer

1. Remove 1 vial from the foil pouch.
2. Twist cap off vial and squeeze contents into nebulizer reservoir.
3. Connect nebulizer reservoir to the facemask/mouthpiece
4. Connect nebulizer to the compressor.
5. Sitting upright, in a comfortable position, place mouthpiece into mouth and turn on compressor.
6. Breathe slowly and regularly until no more mist is in the nebulizer chamber.

To clean weekly

1. Remove the mask/mouthpiece from the reservoir. Remove the tubing and set it aside. The tubing should not be washed or rinsed. Wash the mask/mouthpiece with a mild dishwashing soap and warm water.
2. Rinse under a strong stream of water for 30 seconds.
3. Rinse the nebulizer parts under warm running water for 1 minute. Use distilled or sterile water, if possible.
4. Shake off excess water and air dry.
5. Put the mask/mouthpiece, reservoir, and tubing back together and connect the device to the compressed air machine. Run the machine for 10 to 20 seconds to dry the inside of the nebulizer thoroughly.
6. Disconnect the tubing from the compressed air machine. Store the nebulizer.
7. Clean the surface of the compressed air machine with a damp, soapy cloth, sponge, or an alcohol or disinfectant wipe. Never place the air compressor in water. Place a cover over the compressed air machine.
15.4 Reminders to Increase Adherence

The goals of COPD treatment are to control disease symptoms, prevent chronic complications related to the disease, and prevent exacerbations. Patient adherence with inhaled medications helps to achieve these goals (GOLD website; Restrepo, 2008). Adherence is concordance between the healthcare provider’s recommendations and the patient’s actual behavior. This concordance requires that the patient assumes an active role in their treatment. Over half of patients with COPD adhere poorly with their treatment regimens (Bender, 2006; Haupt, 2008; Krigsman, 2007a; Krigsman, 2007b; Krigsman, 2007c; Lareau, 2010; WHO website). There are a number of reasons for poor adherence, including: the number of chronic co-morbidities; the number of prescribed medications; decreased adherence over time with chronic use of medications; impaired physical and cognitive function; lack of patient understanding about chronic nature of COPD and use of medications to prevent exacerbations; and discontinuation of medication in response to a decline in symptoms (Dolce, 1991; Krigsman, 2007b; Lareau, 2010; Meckenberg, 2008; Restrepo, 2008). Poor adherence is associated with increased risk of exacerbations and greater healthcare utilization (Isamlia, 2014; van Boven, 2014). Patients who adhere to their treatment regimens >80% of the time survive longer than less adherent patients (Vestbo, 2009).

Medication adherence among patients with COPD is affected by a number of variables related to the patient, the treatment, and society (Bourbeau, 2008; Restrepo, 2008). Patient-related factors include their physical abilities, cognitive function, and mental capabilities. For example, patients with COPD and depression adhere less well with their inhalers than those who are not depressed (DiMatteo, 2007; Lareau, 2010). An important treatment-related factor is the use of multiple inhalers, each of which often has a different inhalation technique. Societal factors include the relationship between the patient and the healthcare provider, access to medications, financial resources, ability to receive adequate inhaler education, and the patient’s familial and social support system.

Assessing medication adherence can be difficult as there is no clear definition of what would be an appropriate level of compliance. A variety of methods to assess adherence have been described, including pill counting or weighing, reviewing pharmacy records, patient self-reporting, estimations made by the healthcare provider, electronic monitoring, and biological monitoring (Lareau, 2010). Each of these have their advantages and disadvantages.

Providers can perform a variety of interventions to increase inhaler adherence in patients with COPD. One of the most important factors is effective communication between the healthcare provider and the patient, as low patient satisfaction with their physician is associated with decreased adherence (George, 2005; Restrepo, 2008). Proper inhaler education for the patient is paramount in helping patients understand their drug regimen, and the reasons for taking the medication (Falvo, 1980; George, 2007; Hulka, 1976). Healthcare providers must also be well-educated
about COPD treatment guidelines to educate their patients about all aspects of their disease. Adherence can also be improved by tailoring drug therapy to each patient’s needs, preferences, and capabilities. Patients who are unable to use their inhalers regularly or have complex medication regimens may benefit from simplified, once-daily treatments if possible (Breekveldt-Postma, 2007). Patients who also forget to take medications might benefit from behavioral therapy, such as cueing (for example, placing inhaler on the nightstand) and self-monitoring. Patients who have issues with depression, anxiety, or cognitive impairment should be given written instructions on medication use, as they are prone to have difficulty remembering instructions. Finally, patients who intentionally do not take medication can benefit from further education, review of patient’s personal goals of therapy, and medication negotiation with the patient.

15.5 Conclusions

In this chapter we have discussed commonly used inhalers and how to use them correctly, the importance of inhaler education for correct inhaler technique, and how to increase inhaler compliance / adherence. There are various advantages and disadvantages associated with each type of inhaler. Inhaler device selection depends on the type of medication selected, as well as the patient’s preferences and abilities. The healthcare provider should have adequate knowledge of the inhalational devices being prescribed. Inhaler education including the correct steps to use the device should be provided to the patient when receiving the inhaler, and should be re-addressed at follow-up visits. If medication adherence is an issue, the healthcare provider should search for reasons why, and intervene. Finally, successful inhaler education and adherence rely on effective communication between the healthcare provider and the patient.

15.6 Summary Points

1. Providers should know how to use inhaled medications for COPD correctly, as well as educate patients with COPD how to use their medications appropriately.
2. Repetitive inhaler education and direct observation of inhaler technique should occur in patients with COPD.
3. A pressurized metered-dose inhaler (pMDI) should be used with a spacer. If the patient does not use a spacer, then we recommend the open-mouth technique for pMDI use (Table 15.3).
4. Nebulizers can be used as an alternative to short acting bronchodilator pMDIs when patients cannot use a pMDI properly or when they are hospitalized. A sig-
significant clinical therapeutic difference has not been shown between medications delivered by pMDI with a spacer versus a nebulizer.

5. Inhaler adherence should be addressed by the provider at every patient encounter.

References

Ahrens, R., Lux, C., Bahl, T., & Han, S.H. (1995). Choosing the metered dose inhaler spacer or holding chamber that matches the patient’s need: evidence that the specific drug being delivered is an important consideration. *J Allergy Clin Immunol, 96*(2), 288–294.


16 Management of Outpatient COPD Exacerbations

Key Points
1. COPD exacerbations are associated with an acute worsening of the underlying respiratory symptoms and chronic pulmonary and systemic inflammatory processes.
2. Patients may have a susceptibility phenotype that determines their propensity for exacerbations.
3. Patients with COPD can tell when their baseline symptoms are worsening and can recognize the increases in dyspnea, changes in nature and frequency of cough and sputum, and tachypnea.
4. Early recognition and treatment improves outcomes of COPD exacerbations.
5. Most COPD exacerbations can be safely managed at home with an action plan.
6. Management involves the use of bronchodilators (short acting beta agonists and anticholinergics), steroid therapy, and antibiotics.
7. Between 30% and 50% of COPD exacerbations are associated with a bacterial infection and benefit from antibiotic therapy; antibiotics should be rotated to minimize development of antibiotic resistance.

16.1 Introduction

Chronic obstructive pulmonary disease is an incurable but treatable long term condition that is usually associated with an insidiously progressive loss of lung function and increasing respiratory and systemic symptoms. The course of COPD is often marked by intermittent exacerbations: episodes of increased respiratory symptoms, especially cough, wheezing, phlegm production, and breathlessness, that vary in severity, frequency, duration, and consequence. (See Chapter 9, Natural History, Phenotypes, and Gender Differences in COPD.)

COPD exacerbations may profoundly affect an individual’s health and quality of life and, collectively, exacerbations are the major contributor to the socioeconomic and health-related burden of COPD. Therefore, the treatment and prevention of COPD exacerbations are critical elements in COPD management.

Approximately half of all COPD exacerbations are not reported to healthcare providers and usually are not treated (Wilkinson, 2004). Individuals with COPD may exhibit therapeutic paralysis, attempt to “tough it out” during exacerbations, and do not seek medical attention (Mulhall, 2013). Patients with COPD delay treatment initiation by a median duration of 3.7 days even though each day without treatment prolongs the recovery time by nearly half a day (Wilkinson, 2004). Additionally, those individuals who report exacerbations and are treated have a better quality of life com-
pared with those not treated (Wilkinson, 2004). Thus, although nearly half of all exacerbations are unreported and untreated, earlier recognition and treatment of COPD exacerbations may improve recovery and quality of life.

### 16.2 Definition and Differential Diagnosis

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) report defines a COPD exacerbation as an acute event characterized by a change/increase in the patient’s baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variation (Global initiative for chronic Obstructive Lung Disease (GOLD) guidelines, 2014). Because these symptoms are not specific and may be caused by numerous processes, other causes should be considered during the initial evaluation including myocardial ischemia, heart failure, pneumonia, pneumothorax, pleural effusion, cardiac dysrhythmias, and pulmonary embolism.

In addition to being subjective, the respiratory symptoms that define a COPD exacerbation are patient dependent. To provide more objective measures of COPD exacerbations, various surveys such as the Exacerbations of Chronic Obstructive Pulmonary Disease Tool, a patient-reported outcome (EXACT-PRO), have been developed (Mohan, 2014). The EXACT-PRO is a 14 question survey that is valid and reliable for the objective recognition of COPD exacerbations (Mohan, 2014).

### 16.3 Prevalence

Using a definition of COPD exacerbation as an event treated with antibiotics and/or corticosteroids, the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study monitored exacerbations among 2,138 patients with varying COPD severity for 3 years (Hurst, 2010). During the first study year, the overall exacerbation rate was 1.21 exacerbations/participant and correlated with the severity of airflow limitation: 0.85, 1.34, and 2.00 exacerbations/participant for GOLD stages 2, 3, and 4, respectively (Hurst, 2010). 29% of the study participants had two or more exacerbations in the first year and this proportion increased with disease severity, 22%, 33%, and 47% for GOLD stages 2, 3, and 4, respectively (Hurst, 2010). Approximately half of the patients did not have an exacerbation during the first year. The propensity or resistance to COPD exacerbations was remarkably consistent throughout the study; 71% of patients who had two or more exacerbations in years 1 and 2 had frequent exacerbation in year 3 and 74% of those with no exacerbations in years 1 and 2 had no exacerbations in year 3. Frequent exacerbations were associated with a history of prior events, gastroesophageal reflux or heartburn, worse quality of life, and increased white blood cell count (Hurst, 2010). Thus, the annual frequency of COPD exacerbations ranges from approximately one quarter to one half of individuals.
Etiology

COPD exacerbations are characterized by increased inflammation of the entire tracheobronchial tree with increased numbers of macrophages and CD8 T lymphocytes in the airway wall and neutrophils in the airway lumen. Systemic inflammation is also elevated (Wedzicha, 2007). Persistently elevated levels of C reactive protein (CRP) after an exacerbation are associated with failure to recover from that episode and portend another exacerbation within 50 days (Wouters, 2005; Perera, 2007). Elevation of fibrinogen levels is associated with the presence and frequency of COPD exacerbations (Duvoix, 2013). Other biomarkers include procalcitonin and peripheral blood eosinophil count (Brightling, 2013). Elevated levels of von Willebrand’s factor, D dimer, and prothrombin fragment 1+2 during COPD exacerbations suggest damage to endothelial cells and activation of clotting cascades (Polosa, 2011).

70–80% of COPD exacerbations are triggered by respiratory infections, mainly viral and bacterial and the majority of the rest are due to environmental exposures and medication non-adherence (Sethi, 2008). The risk of admission for COPD exacerbation is correlated with the severity of the underlying COPD (Bahadori, 2007) and these risk factors are presented in Table 16.1.

Table 16.1: Risk factors for COPD exacerbation hospitalization and readmission (Bahadori, 2007)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Increased $P_{CO_2}$</td>
<td>Increased risk of COPD hospitalization, readmission and reduced survival</td>
</tr>
<tr>
<td>2. Lower FEV$_1$</td>
<td>Increased risk of COPD hospitalization and readmission</td>
</tr>
<tr>
<td>3. Prior COPD exacerbations</td>
<td>3 or more times in the preceding year is associated with Increased risk of readmission</td>
</tr>
<tr>
<td>4. Inhaled corticosteroid use</td>
<td>Associated with increased risk of COPD hospitalization.</td>
</tr>
<tr>
<td>5. Oral corticosteroid use</td>
<td>Associated with increased risk of COPD hospitalization and readmission</td>
</tr>
<tr>
<td>6. Reported poor health related quality of life</td>
<td>Associated with increased risk of COPD hospitalization</td>
</tr>
<tr>
<td>7. Long term use of oxygen</td>
<td>Associated with increased risk of COPD hospitalization and readmission</td>
</tr>
<tr>
<td>8. History of COPD</td>
<td>5 years is associated with a doubling in the risk of readmission</td>
</tr>
<tr>
<td>9. Co-existing comorbidities</td>
<td>Including coronary artery disease, congestive heart failure, or diabetes</td>
</tr>
<tr>
<td>10. Severe dyspnea</td>
<td>Increased risk of COPD hospitalization and readmission</td>
</tr>
</tbody>
</table>

with COPD depending upon the severity of their airflow limitation and the propensity toward frequent or infrequent exacerbations is stable over a several year period.

16.4 Etiology
16.5 Presentation

Exacerbations are associated with an acute worsening of a patient’s health status and delay in treatment is associated with slower resolution and increased risk of hospitalization (Wilkinson, 2005). Consequently, a patient’s early recognition of exacerbation symptoms and prompt treatment improves exacerbation recovery, reduces risk of hospitalization, and is associated with better health-related quality of life. Patients with COPD can recognize the worsening of their baseline symptoms with each exacerbation and can learn to identify these symptoms. The symptoms depend on the cause of the exacerbation and typical manifestations include cough, sputum production, dyspnea, tachypnea, wheezing, and a decrease in pulmonary function. (Table 16.2)

Table 16.2: Respiratory Symptoms During a COPD Exacerbation

| 1. Greater dyspnea, especially with exertion |
| 2. Increase in frequency and severity of cough |
| 3. Changes in sputum production including increased volume, purulence, and blood |
| 4. Tachypnea |
| 5. Wheezing |

Physical examination findings depend on the severity of the exacerbation and typically include wheezing and tachypnea. In more severe exacerbations, patients develop difficulty speaking, use accessory respiratory muscles, and exhibit paradoxical chest and abdominal wall movements due to asynchrony between the chest and abdomen with respiration. In very severe exacerbations, patients develop hypoxemia and hypercapnia with an increase in lethargy and possible obtundation. They may have fever, chills, or night sweats if there is a precipitating bacterial infection.

16.6 Natural History

The median recovery time from a COPD exacerbation is 6 days for the peak expiratory flow rate (PEFR) and 7 days for daily symptoms; up to 14% of patients do not recover clinically within 35 days and some never return to baseline (Seemungal, 2000). PEFR recovery to baseline values is complete in only 75.2% of exacerbations at 35 days and, in 7.1% of exacerbations, PEFR recovery has not occurred by 91 days (Seemungal, 2000). The rate of decline in forced expiratory volume in one second (FEV₁) is 2–8 ml/year greater in frequent COPD exacerbators (two or more exacerbations yearly) compared with infrequent exacerbators (less than two exacerbations annually) (Donaldson, 2002; Vestbo, 2011). Quality of life is significantly affected by COPD exacerbations and, as measured by the St. George’s Respiratory Questionnaire
Outpatient Management of COPD Exacerbations

16.7 Consequences

The consequences of ambulatory COPD exacerbations are less well studied than more severe exacerbations requiring healthcare encounters but are associated with poor outcomes (Table 16.3).

**Table 16.3: Consequences of Frequent COPD Exacerbations (Qureshi, 2014; Chhabra, 2014)**

<table>
<thead>
<tr>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased risk of future exacerbations</td>
</tr>
<tr>
<td>Greater mortality</td>
</tr>
<tr>
<td>More frequent healthcare visits</td>
</tr>
<tr>
<td>Faster decline in lung function</td>
</tr>
<tr>
<td>More inflammation</td>
</tr>
<tr>
<td>Worse quality of life</td>
</tr>
<tr>
<td>Less physical activity</td>
</tr>
<tr>
<td>Aggravation of co-morbidities</td>
</tr>
</tbody>
</table>

16.8 Outpatient Management of COPD Exacerbations

16.8.1 Indications for Home Care

Patients with COPD can recognize the worsening of their baseline symptoms that characterize exacerbations. Common symptoms include a cold or flu, feeling run down or tired, and mood changes, such as feeling down or anxious. When these symptoms are associated with cardinal COPD symptoms including increased shortness of breath and increased amounts of cough and sputum and/or sputum changes from its normal color to a yellow, green or rust color, it is strongly suggestive of a COPD exacerbation. Patients should be given an action plan that explains how to manage exacerbations at home (Figure 16.1 and Table 16.4). The action plan is filled out by the health care provider during routine visits and is individualized for each patient. It includes a list of symptoms to aid the patient in recognizing and assessing the severity of his/her symptoms and lists appropriate next steps.

Other steps include reducing activity, resting frequently, and practicing controlled breathing and relaxation. After resolution of an exacerbation, the patient should see
Table 16.4: Components of a COPD action plan

1. Assessment of symptoms and their severity
2. Assessment of the need to inform primary care provider of symptoms or seek more acute medical care
3. Patient initiates prescribed prednisone
4. Patient starts prescribed antibiotic
5. Patient takes 2–4 puffs of their rescue inhaler (albuterol) as needed, up to 4 to 8 times per day for shortness of breath
6. Information about when to seek further medical care

When you have a COPD exacerbation
1. Start your action plan as instructed by your Provider
2. If you do not feel better after 48 hours, or if you are getting worse at any time, seek medical attention immediately.
3. Schedule an appointment to see your Provider or contact your Provider to refill and maintain your COPD exacerbation medications—inhalers, antibiotics, and steroids at all times.

Assessment of COPD Disease Activity

<table>
<thead>
<tr>
<th>I am doing well today</th>
<th>Symptoms</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual activity and exercise level</td>
<td>Take daily medicines</td>
<td></td>
</tr>
<tr>
<td>Normal amounts of cough or sputum</td>
<td>Use oxygen as prescribed</td>
<td></td>
</tr>
<tr>
<td>Typical level of breathlessness at rest and with exertion</td>
<td>Continue regular exercise/diet plan</td>
<td></td>
</tr>
<tr>
<td>Sleeping well at night</td>
<td>Avoid cigarette smoke and other irritants</td>
<td></td>
</tr>
<tr>
<td>Appetite is good</td>
<td>Plan activities and pace yourself</td>
<td></td>
</tr>
</tbody>
</table>

I am having a bad day or COPD Exacerbation

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>More wheezy and breathless than usual</td>
<td>Continue daily medications and oxygen</td>
</tr>
<tr>
<td>Feeling run down or tired</td>
<td>Use quick relief inhaler (albuterol) 2-4 puffs with spacer every 2-4 hours</td>
</tr>
<tr>
<td>Increased cough or sputum; change in color of sputum</td>
<td>Start an oral corticosteroid (Prednisone 40 mg orally daily for 5 days)</td>
</tr>
<tr>
<td>Utilizing more reliever medication (albuterol) than usual</td>
<td>Start an antibiotic (Use most recently prescribed antibiotic; see chart below)</td>
</tr>
<tr>
<td>Swelling of ankles more than usual</td>
<td>Use pursed lip breathing</td>
</tr>
<tr>
<td>Poor sleep or loss of appetite</td>
<td>Use anxiety/stress management techniques</td>
</tr>
<tr>
<td>Cold or flu symptoms</td>
<td>Reduce activity and rest frequently</td>
</tr>
<tr>
<td>Feeling down or increased anxiety</td>
<td>Eat and drink well especially fluids</td>
</tr>
<tr>
<td>Recent weather change or exposure to air pollution or smog</td>
<td>Call provider if symptoms don’t improve after 48hrs or if you develop any of the symptoms listed below.</td>
</tr>
</tbody>
</table>

I need urgent medical attention

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danger Signs – Severe breathlessness, chest pain, fever, agitation, fear, drowsiness, confusion</td>
<td>Call 911 or seek medical care immediately</td>
</tr>
<tr>
<td>Severe shortness of breath even at rest</td>
<td>Show them this plan and say you have severe COPD</td>
</tr>
<tr>
<td>Not able to perform normal activities</td>
<td></td>
</tr>
<tr>
<td>Not able to sleep because of breathing</td>
<td></td>
</tr>
<tr>
<td>Fever or chills</td>
<td></td>
</tr>
<tr>
<td>Feeling confused or very drowsy</td>
<td></td>
</tr>
<tr>
<td>Chest discomfort/pain</td>
<td></td>
</tr>
<tr>
<td>Coughing up blood</td>
<td></td>
</tr>
</tbody>
</table>

Antibiotic Rotation
After a COPD exacerbation, a different antibiotic may need to be prescribed for your next exacerbation. Help your doctor do this by keeping track of the name of the antibiotic, and when you started taking it for each COPD exacerbation. Bring this information with you to your doctor appointments.

<table>
<thead>
<tr>
<th>Antibiotic Name</th>
<th>Date Antibiotic Taken</th>
</tr>
</thead>
</table>

Figure 16.1: Generic COPD Action Plan (American Lung Association accessed December, 2014; Australian Lung Foundation accessed December, 2014; Canadian Medical Association accessed December, 2014)
Management

their primary care provider to obtain a different antibiotic to ensure antibiotic rotation for the next exacerbation (Postma, 1999) and minimize development of antibiotic resistance. A generic action plan derived from recommendations from the American Lung Association, the Canadian Medical Association, and the Australian Lung Foundation (American Lung Association accessed December, 2014; Australian Lung Foundation accessed December, 2014; Canadian Medical Association accessed December, 2014) is presented in Figure 16.1.

16.8.2 Indications for a Healthcare Encounter

Patients who are extremely breathless, anxious, panicky, confused, agitated, fearful, or drowsy should seek immediate medical attention. Other patients should start with the action plan but if there is no improvement after 48 hours, or if symptoms worsen at any time, medical attention should be sought immediately (GOLD guidelines, 2014). Other indications to escalate the level of care are presented in Table 16.5.

16.9 Management

16.9.1 Home Care

A COPD action plan (Figure 16.1) encourages early intervention by giving patients guidelines to enhance the recognition of an exacerbation and how to initiate early medical management. Action plans with limited or no self-management education (See Educational Programs below) promote patient recognition and initiation of treat-
Management of Outpatient COPD Exacerbations

Antibiotics
- Doxycycline
- Trimethoprim-sulfamethoxazole
- Amoxicillin and clavulanate
- Macrolides – Clarithromycin, Azithromycin
- Fluoroquinolones – Levaquin, Gatifloxacin, Moxifloxacin

Antibiotics
- Ceftriaxone, Cefotaxime, Ceftazidime
- Antipseudomonal penicillins – Piperacillin-tazobactam, Ticarcillin-clavulanate
- Fluoroquinolones – Levofloxacin, Gatifloxacin
- Aminoglycoside – Tobramycin

Figure 16.2: COPD management algorithm, modified from Anthonisen (1987), Hunter (2001) and Siddiqi (2008)

For COPD exacerbations but have not been demonstrated to decrease healthcare utilization or improve health-related quality of life (Walters, 2010). The action plan contains advice on how to increase the use of routine COPD medications, to use breathing exercises and relaxation techniques, to change the environment if it is causing the exacerbation, and to increase oxygen use. If the exacerbation is infectious and the dyspnea is accompanied by increased or colored sputum, antibiotics and systemic steroids are indicated (see Figure 16.2). If the condition worsens, patients are advised to visit their physician's office or the emergency department. Follow-up with their physicians either in person or via telephone or electronic communication after the episode is also recommended. Medications used to treat a COPD exacerbation
are reviewed in Table 16.6. Adherence to a written action plan is associated with a reduction in exacerbation recovery time (Bischoff, 2011). Knowing the factors that are associated with proper and prompt utilization of an action plan permits healthcare professionals to direct self-management support to appropriate patients. For those individuals who are unable to adhere with a self-administered action plan, an intensive home care program, including nurse visits, home oxygen, and physical therapy, produces clinical outcomes that are equivalent to hospitalization (Postma, 1999). See discussion of hospital at home below.

Table 16.6: Pharmacologic therapy in acute exacerbation (Updated from Stoller, 2002)

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Mode of Delivery</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchodilators</td>
<td>Beta-adrenergic agonist</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Albuterol</td>
<td>Metered-dose inhaler or Nebulizer</td>
<td>100–200 µg 0.5–2.0 mg</td>
<td>4–8 times daily</td>
</tr>
<tr>
<td></td>
<td>Ipratropium bromide</td>
<td>Metered-dose inhaler or Nebulizer</td>
<td>18–36 µg 0.5 mg</td>
<td>4 times daily</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Prednisone</td>
<td>Pill</td>
<td>30–60 mg</td>
<td>Daily for 5 days</td>
</tr>
</tbody>
</table>

16.9.2 Bronchodilators

16.9.2.1 Short Acting Bronchodilators

**Beta adrenergic agonists**: Inhaled short-acting beta adrenergic agonists (SABA e.g. albuterol) are the mainstay of therapy for an acute exacerbation due to their rapid onset of action and efficacy in producing bronchodilation. After inhalation, the effects of SABAs begin within 5 minutes and reach maximal effect at 30 minutes. SABA’s improve FEV₁ and FVC by 15 to 29% over a period of 60 to 120 minutes. Side-effects include tremors, headache, nausea, vomiting, palpitations, heart rate, and blood pressure variations. There is no added benefit to adding long acting beta-adrenergic agents (LABA e.g. salmeterol) in the treatment of acute exacerbations. Nebulizers and metered dose inhalers (MDI) with spacers have equal efficacy during exacerbations but patients may have difficulty with proper MDI technique during an exacerbation. There has been no demonstrated advantage to the use of a higher cumulative dose of albuterol in patients with acute exacerbation of COPD and 4 times daily dosing is usually adequate (Emerman, 1997).
**Anticholinergic agents:** Anticholinergic agents (non-selective muscarinic antagonists-SAMA e.g. ipratropium bromide) have an equivalent effect to SABA’s and other factors such as the time to peak effect (slightly more rapid for SABA’s) and the frequency of adverse effects (fewer and milder with ipratropium bromide – tremors, dry mouth, and urinary retention) may influence the choice of agent for a given patient (Karpel, 1990; Rebuck, 1997; Johnson, 2002). Ipratropium’s effect begins within 10–15 minutes and peaks at 30–60 minutes.

The effects of the two classes of short acting bronchodilator agents decline after 2–3 hours but can last as long as 4–6 hours. Both inhaled agents are more effective than all parenterally administered bronchodilators (methylxanthines and sympathomimetics). Unlike the management of stable COPD where the concurrent administration of albuterol and ipratropium is more efficacious than either agent given alone (The COMBIVENT Inhalation Solution Study Group, 1997), a combination of short acting bronchodilators given sequentially in exacerbations does not provide additional benefit (Karpel, 1990; Patrick, 1990; Moayyedi, 1995).

### 16.9.3 Corticosteroid Therapy

Several randomized, placebo-controlled trials have demonstrated the benefit of systemic corticosteroid therapy in accelerating improvement in airflow, gas exchange, and symptoms, and in reducing the rate of treatment failure (Albert, 1980; Thompson, 1996; Aaron, 2003; Niewoehner, 1999; Aaron, 2003; Davies, 1999; Maltais, 2002). Benefits include a higher FEV$_1$ on day 1, lower rate of treatment failure at 30 and 90 days, and a shorter hospital stay. The optimal duration of therapy remains uncertain but some studies support a course of 5–10 days (Davies, 1999; Sayiner, 2001; Stanbrook, 2001). Patients with COPD exacerbations continue to have cumulative improvement in FEV$_1$ during a 10 day corticosteroid course. However, outcomes were no better with an 8 week course of corticosteroids compared with a 15 day course. A Cochrane review found no significant increase in treatment failure with shorter systemic corticosteroid treatment for seven days or less for acute exacerbations of COPD (Walters, 2011). More recently, the REDUCE trial demonstrated that 5 days was not inferior to 14 days of oral 40 mg prednisolone daily and there were no differences in time to the next exacerbation, mortality, restoration of lung function, and adverse events during the 6 months of follow up (Leuppi, 2013).

Oral glucocorticoids are rapidly absorbed with peak serum levels achieved at one hour after ingestion with virtually complete bioavailability. They are as efficacious as intravenous glucocorticoids for treating most exacerbations unless the patient is unable to take oral medications or has poor gastrointestinal absorption.

Most exacerbations can be treated with 30–60 mg prednisone daily for 5–7 days (Gold Guidelines, 2014) and steroid therapy can be stopped without tapering if the duration of therapy is less than 3 weeks (Gold Guidelines, 2014; Niewoehner, 1999).
Longer durations of therapy have no added benefit and a higher risk of adverse effects especially hyperglycemia. More recent findings are suggesting that shorter durations with lower doses are as effective as longer courses with higher doses of corticosteroids.

16.9.4 Antibiotic Therapy

Up to 50% of COPD exacerbations are associated with bacterial infections and antibiotics are indicated for these patients. Clinical criteria (increased dyspnea, sputum volume and sputum purulence) are sufficient to commence a course of antibiotics for a COPD exacerbation and sputum cultures are not usually obtained unless there is a clinical indication. Treatment is usually empirical and a low-cost antibiotic such as trimethaprim-sulfamethoxazole, azithromycin, cefuroxime, or tetracycline is adequate for mild exacerbations in relatively uncompromised patients. For more severe exacerbations, a broader-spectrum antibiotic such as moxifloxacin or levofloxacin that is effective against resistant strains of H. influenzae and S. pneumoniae is recommended. Patients with systemic symptoms such as pneumonia should be treated with a broad-spectrum antibiotic. See Figure 16.2.

16.9.5 Chronic Antibiotic Treatment

Long term antibiotic treatment with azithromycin, erythromycin, clarithromycin, or moxifloxacin has been demonstrated to reduce COPD exacerbations (Herath, 2013). A meta-analysis demonstrated an odds ratio of 0.55 (95% CI, 0.39–0.77) for COPD exacerbations with prophylactic antibiotic treatment and the number needed to treat was 8 (95% CI, 5–18) (Herath, 2013). Both azithromycin and erythromycin have been studied extensively and reduce the time to first exacerbation and exacerbation frequency when administered daily for one year but also adversely impair hearing and increase the prevalence of macrolide resistant bacteria in the sputa of treated patients (Ramos, 2014). Azithromycin therapy has also been associated with a prolonged QTc. (Albert, 2011). The benefit of macrolides has to be balanced against the possible development of antibiotic resistance both in the patient being treated and in other individuals. The exact mechanism of action of macrolides is not known but may be related to their antibacterial, anti-inflammatory, or immunomodulating properties (Martinez, 2008).

16.9.6 Phosphodiesterase 4 (PDE 4) Inhibitors

PDE-4 inhibitors, roflumilast and cilomilast, reduce inflammation and bronchoconstriction by preventing the degradation of cyclic AMP by phosphodiesterase (Beghe,
2013). PDE-4 inhibitors reduce the frequency of COPD exacerbations (OR 0.77, 95% CI 0.71, 0.83) with a number needed to treat for an additional benefit, 20 (95% CI, 16 to 27) (Chong, 2013). Adverse effects of the PDE-4 inhibitors include gastrointestinal symptoms, headache, and weight loss.

16.9.7 Oxygen Therapy

Alterations in oxygenation during COPD exacerbations appear to be associated with the severity of the exacerbation. A prospective study of 40 individuals with moderate to severe COPD not receiving supplemental oxygen demonstrated that the stable mean SpO$_2$ was 94.8% with a standard deviation of 1% (Hurst, 2010). The maximum reduction in the SpO$_2$ standard deviation during an exacerbation was only 1.24% suggesting that the SpO$_2$ did not decline markedly during less severe exacerbations. In contrast, in a prospective study of 2,487 patients presenting to an emergency department with a COPD exacerbation, half had an oxygen saturation < 90% (Quintana, 2014).

Patients with COPD exacerbations are given oxygen to treat hypoxemia with a goal of maintaining adequate levels of oxygenation without precipitating respiratory acidosis or worsening hypercapnia (Brill, 2014). The minimal adequate or safe level of oxygenation has not been defined definitively but most experts suggest a target SpO$_2$ range of 88–92% (Brill, 2014). The administration of oxygen has potential therapeutic benefits, which include relief of pulmonary vasoconstriction, decrease in right heart strain, and improved myocardial oxygenation. A high F$\text{O}_2$ is not required to correct the hypoxemia associated with most acute exacerbations and persistent hypoxemia should prompt consideration of pulmonary embolism (PE), acute respiratory distress syndrome (ARDS), pulmonary edema, or severe pneumonia. Oxygen delivery devices include face masks, Venturi masks, nasal cannulae, and non-rebreathing masks. Simple face masks can provide a F$\text{O}_2$ up to 55% and nasal cannulae up to 40%. Venturi masks provide a precise F$\text{O}_2$ from 24% to 60% and are the preferred means of oxygen delivery. Non-rebreathing masks can deliver a F$\text{O}_2$ up to 90%.

Although a “more is better” approach to supplemental oxygen has been adopted by many providers, recent evidence suggests that hyperoxemia (defined as a SpO$_2$ greater than the target range of 88–92%) is harmful. A British study demonstrated that lower flow oxygen (F$\text{O}_2$ < 28%) with a goal SpO$_2$ 88–92% compared with higher flow oxygen delivered while transporting patients with COPD to the hospital reduced the proportion of complicated admissions (defined as the need for aminophylline, invasive or noninvasive ventilation, or death) to 25.2% from 40.8% (Durrington, 2005). In a prospective study comparing untitrated high flow oxygen with oxygen titrated to a target SpO$_2$ 88–92%, titrated oxygen reduced mortality among those participants with COPD by 78% and among all participants by 58% (Austin, 2010). In patients presenting to an emergency department, hyperoxemia (PaO$_2$>100 mmHg) was associ-
ated with a greater risk of adverse outcomes (hypercapnic respiratory failure, assisted ventilation, or death) OR 9.17 (95% CI, 4.08, 20.6) than hypoxemia (PaO$_2$<60 mm Hg) OR 2.16 (95% CI, 1.11, 4.20) (Cameron, 2012).

In patients who do develop hypercarbia after treatment with higher levels of oxygen, rapid cessation of supplemental oxygen may lead to “rebound hypoxemia” due to a greater reduction in the arterial oxygen level compared with the arterial carbon dioxide level upon oxygen withdrawal (Kane, 2011). Therefore, in patients who develop oxygen induced hypercarbia, treatment with invasive or noninvasive ventilation while maintaining low concentration supplemental oxygen should be considered.

### 16.9.8 Educational Programs

Multiple and varied self-management programs for patients with COPD have been developed and implemented with widely ranging results. A review of COPD educational programs revealed that 53.8% of programs incorporated 10 or more areas of instruction (Stoilkova, 2013). The most common topics were smoking cessation (80.0%), medications (76.9%), exercise (76.9%), breathing techniques (70.8%), exacerbations (69.2%), and stress management (67.7%). Most programs were led by nurses (75.8%) who supplied written information (90.5%) and utilized demonstrations or practice sessions (73.8%). A Cochrane meta-analysis demonstrated that self-management education for patients with COPD reduced hospitalizations, OR 0.57 (95% CI 0.43, 0.75) with a number needed to treat 8 (95% CI, 5, 14) for those with high risk of COPD hospitalization and 20 (95% CI, 15, 35) for those with low risk (Zwerink, 2014). Additional benefits included enhanced quality of life and reduced breathlessness. Integrated disease management incorporating a multidisciplinary team improves quality of life, reduces breathlessness, increases the distance walked in 6 minutes, and decreases the number of hospitalizations and hospitalization duration (Kruis, 2013). A randomized control trial of a Comprehensive Care Management program to prevent COPD hospitalizations (Fan, 2012) did not demonstrate decreased hospitalizations and was associated with unanticipated excess mortality. This finding may have been related to differences between patients not detectable in data or possibly to undetected delays in care in the intervention group due to a false sense of security.

### 16.9.9 Hospital at Home

An alternative to hospitalization for an acute COPD exacerbation is hospital at home, a program of intensive management of COPD exacerbations in a patient’s home by visiting healthcare providers. A meta-analysis of patients presenting to the emergency department and then treated with hospital at home for COPD exacerbations
demonstrated a reduction in readmission rates compared with traditional hospitalization, RR 0.76 (95% CI, 0.59, 0.99) and a trend toward reduced mortality, RR 0.65 (95% CI, 0.4, 1.04) (Jeppesen, 2012).

16.9.10 Respiratory stimulants

Respiratory stimulants, measures to increase mucous clearance such as acetylcysteine, nebulized magnesium, and chest physiotherapy are not beneficial in acute exacerbations.

16.10 Prevention of COPD Exacerbations

16.10.1 Pulmonary Rehabilitation

Pulmonary rehabilitation is a multidisciplinary intervention that combines education and exercise to optimize physical conditioning, adherence, and patient involvement in care (Spruit, 2006). When provided in either the stable state or after an acute exacerbation, pulmonary rehabilitation is a highly effective and safe intervention to reduce hospital admissions and mortality and to improve health-related quality of life in COPD patients (Spruit, 2014; Lacasse, 2006; Puhan, 2011). A meta-analysis of pulmonary rehabilitation after a COPD exacerbation revealed reduced mortality (OR 0.28, 95% CI 0.10, 0.84), fewer hospitalizations (OR 0.22, 95% CI 0.08, 0.58) with a number need to treat 4 (95% CI, 3 to 8), and improved quality of life and exercise capacity (Puhan, 2011).

16.10.2 Smoking cessation

A cohort study of 23,971 self-reported previous and current smokers demonstrated that quitting smoking is associated with fewer COPD exacerbations, HR 0.78, (95% CI 0.75,0.87) and that the effect depends upon the length of smoking cessation, 1.04 at less than one year to 0.65 at 10 or more years of smoking abstinence (Au, 2009). Smoking cessation but not smoking reduction is associated with fewer COPD hospitalizations, HR 0.57 (95% CI, 0.33, 0.99) and 0.93 (95% CI, 0.73, 1.18), respectively (Godtfredsen, 2002).
16.10.3 Nutritional support

Although low body mass index and weight loss are risk factors for COPD exacerbations, the effect of nutritional supplementation on exacerbation frequency is not well studied (Hallin, 2006). A meta-analysis showed that nutritional supplementation stimulates weight gain in patients with COPD and the effect is greatest in malnourished patients (Ferreira, 2012). Additional benefits of nutritional supplementation included increases in measures of fat-free body mass, respiratory muscle strength, distance walked in 6 minutes, and health-related quality of life (Collins, 2013; Ferreira, 2012).

16.10.4 Lung Volume Reduction Surgery (LVRS)

In patients who are appropriate candidates, LVRS reduces severe COPD exacerbations (respiratory-related emergency room visits and hospitalizations) by 29% (95% CI, 11–48%) compared with medical management (Washko, 2008). LVRS also increases the time to the first COPD exacerbation in patients with and without a history of exacerbations in the year prior to surgery (Washko, 2008).

16.10.5 Telehealth

Clinical information systems can monitor patients with COPD in their homes using biosensors and questionnaires. This information is transmitted to a central coordination center and reviewed by healthcare providers using data processing algorithms and alerts to monitor daily status, advise individual patients about the goals of maintenance of maximal function and independence, early detection and management of exacerbations and reducing in-person healthcare visits, and provide pulmonary rehabilitation (Goldstein, 2014; McKinstry, 2013). Use of telehealth services for patients with COPD reduces emergency room visits and hospitalizations and exacerbations, does not improve quality of life, and has no effect or may actually increase mortality rates by delaying needed in person care (Kamei, 2013; McLean, 2012; Polisena, 2010). A cost effectiveness review of telehealth for chronic conditions including COPD concluded that telehealth was not cost effective when added to usual care (Henderson, 2013).

16.11 Risk Factors for Relapse

Risk factors for relapse include patients requiring increased doses of nebulized bronchodilators, use of theophylline, use of supplemental oxygen at home, an ED visit in
the preceding week, number of ED and urgent care visits in the past year, self-reported activity limitation, respiratory rate at ED presentation, prior relapse after a hospital visit, and preceding use of glucocorticoids or antibiotics (Kim, 2004). Proven interventions that minimize relapse include smoking cessation, pulmonary rehabilitation, and physical exercise. (See prior sections.) Other strategies to prevent relapse of exacerbations are presented in Table 16.7. Tiotropium, a long acting anticholinergic agent that causes prolonged and persistent bronchodilation, reduces COPD exacerbations and COPD-related hospitalization rates (Anzueto, 2009). Long acting beta adrenergic agonists (LABA) such as salmeterol or formoterol reduce the risk of COPD exacerbations by 23% (Puhan, 2009). Inhaled corticosteroids (ICS) have proven efficacy in reducing the number and severity of exacerbations (Alsaeedi, 2002). The combination of LABA and ICS reduces exacerbations by 25% over a one year period (Calverley, 2003).

**Table 16.7: Strategies to Prevent Relapse After an Acute COPD Exacerbation**

<table>
<thead>
<tr>
<th>Pulmonary Rehabilitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking cessation</td>
</tr>
<tr>
<td>Self-management plans</td>
</tr>
<tr>
<td>LABAs: salmeterol, formoterol</td>
</tr>
<tr>
<td>Combination therapy: LABA/ICS</td>
</tr>
<tr>
<td>Tiotropium</td>
</tr>
<tr>
<td>Influenza vaccine</td>
</tr>
<tr>
<td>Physical exercise</td>
</tr>
<tr>
<td>LVRS in selected patients</td>
</tr>
</tbody>
</table>

Abbreviations: LABA: long-acting β 2-agonist; ICS: inhaled corticosteroid; LVRS: lung volume reduction surgery.

16.12 Conclusion

The natural history of COPD is usually punctuated by exacerbations that are characterized by increased respiratory symptoms including breathlessness, cough, wheezing, and sputum production. The frequency, severity, duration, and consequences of each exacerbation vary but patients with COPD appear to exhibit frequent or infrequent exacerbator phenotypes. Nearly half of all exacerbations are not reported by patients but earlier recognition and treatment is associated with more rapid recovery and better quality of life. The main pharmacologic treatments are short acting bronchodilators, antibiotics, and corticosteroids. Factors that reduce relapse of COPD
exacerbations include pulmonary rehabilitation, smoking cessation, long acting anti-cholinergics and beta agonists, and self-management plans.

16.13 Summary Points

1. COPD exacerbations are interspersed throughout the natural course of COPD but some patients are prone to frequent episodes whereas others have few or infrequent exacerbations.
3. The principal pharmacologic treatments of COPD exacerbations are:
   - Short acting bronchodilators
   - Antibiotics which should be rotated to mitigate the selection of resistant bacteria
   - Corticosteroids which are beneficial in moderate doses (prednisone 40 mg/d orally) and short duration (5 days) that do not require tapering
4. Pulmonary rehabilitation after an acute COPD exacerbation improves survival, reduces subsequent hospitalizations, increases exercise capacity, and improves quality of life.
5. Newer modalities for the ambulatory management of COPD exacerbations include hospital at home and telemedicine.

References


Nishant Gupta, MD

17 Inpatient Management of Acute COPD Exacerbations

Key Points
1. Acute exacerbations of COPD are a leading cause of morbidity and mortality worldwide. The majority of acute exacerbations of COPD are triggered by bacterial and viral infections.
2. The presence of severe symptoms (breathlessness, cough, wheezing), hemodynamic instability, hypoxemia or hypercapnia, severe underlying disease/comorbidities, and lack of adequate support at home, are some of the factors which should trigger inpatient management as compared to home management of an acute exacerbation.
3. Supplemental oxygen should be provided to target oxygen saturations between 88 – 92%.
4. Moderate dose glucocorticoids for a short duration (40mg prednisone for 5 days) are sufficient for most patients with an acute exacerbation.
5. Use of Noninvasive Positive Pressure Ventilation (NIPPV) reduces mortality and improves outcomes in hypoxemic/hypercapnic patients with acute exacerbations of COPD, and, unless absolutely contraindicated, should be the modality of choice for ventilatory support.

17.1 Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and lungs to noxious stimuli or gases (Global initiative for chronic Obstructive Lung Disease (GOLD) guidelines, 2014). It represents a major public health challenge. The prevalence and burden of COPD are projected to increase in the coming years due to continued exposure to COPD risk factors and the aging population (Mathers, 2006). In addition to being a leading cause of mortality and morbidity, COPD poses a significant economic and social burden. In the United States, the estimated direct costs from COPD are 29.5 billion dollars and indirect costs are 20.4 billion dollars (NHLBI Mortality & Morbidity chartbook, 2012). The majority of this cost burden is attributable to COPD exacerbations. In the subsequent sections we will review the salient features of COPD exacerbations and the management of hospitalized patients with COPD exacerbations.
17.2 Definition and Risk Factors

A COPD exacerbation is defined as an acute event characterized by worsening of the patient’s respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication (GOLD guidelines, 2014). It is accompanied by a change in one or all of the following symptoms:

1. Increase in cough severity and frequency
2. Change in sputum color or consistency
3. Increase in baseline dyspnea

17.3 Risk Factors for COPD Exacerbations

Multiple studies have attempted to identify factors which might predispose patients to frequent exacerbations. In an observational study, Miravitlles et al (Miravitlles, 2000) found that increasing age, severity of FEV\textsubscript{1} impairment, and presence of chronic mucus hypersecretion were independently associated with the risk of having 2 or more exacerbations per year. Additionally, the severity of FEV\textsubscript{1} impairment and the presence of co-morbid conditions were associated with a higher risk of hospitalization (Miravitlles, 2000). In another study, chronic cough and sputum production were associated with frequent COPD exacerbations including frequent hospitalizations for severe exacerbations (Burgel, 2009). Niewoehner et al (Niewoehner, 2007) created a multi-variate model and found that older age, severity of FEV\textsubscript{1} impairment, productive cough, duration of COPD, hospitalization for COPD in the previous year, and theophylline use at baseline predicted a higher risk of future exacerbations. In the same study, older age, percentage of predicted FEV\textsubscript{1}, unscheduled clinic/emergency department visits for COPD in the prior year, any cardiovascular comorbidity, and prednisone use at baseline were associated with a greater risk of hospitalization (Niewoehner, 2007).

Perhaps the best appraisal of COPD exacerbations comes from the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study (Hurst, 2010). This study followed more than 2000 patients with COPD for a period of 3 years and observed the frequency of COPD exacerbations. They found that exacerbations became more frequent and more severe as the severity of COPD increased. The single best predictor of exacerbations, across all GOLD stages, was a history of prior exacerbations. Other factors associated with an increased frequency of exacerbations were the presence of gastroesophageal reflux disease (GERD), poorer quality of life, and elevated white blood cell (WBC) count (Hurst, 2010).

COPD is frequently characterized by evidence of increased low grade systemic inflammation (Gan, 2004). Recently, Thomsen et al hypothesized that elevated levels of inflammatory biomarkers in patients with stable COPD are associated with an increased risk of exacerbations. They identified 6574 patients with COPD from the
participants of Copenhagen City Heart Study and the Copenhagen General Population Study and followed them prospectively to assess for exacerbations. They found that elevated levels of inflammatory biomarkers at baseline (CRP, Fibrinogen and WBC count) were associated with an increased risk of future exacerbations, even in patients with mild disease and no prior history of exacerbations (Thomsen, 2013).

17.4 Etiology of COPD Exacerbations

COPD exacerbations can be triggered by several factors. The most common cause of an acute exacerbation is a respiratory tract infection (viral or bacterial). Bacterial pathogens are believed to be responsible for up to 50% of the COPD exacerbations (Sethi, 2008). Rosell et al performed bronchoscopic sampling of lower airways and found clinically significant bacterial concentrations in 54% of patients with COPD exacerbations as opposed to 4% of healthy adults (Rosell, 2005). Acquisition of new bacterial strains may play a central role in the pathogenesis of COPD exacerbations (Sethi, 2008). Respiratory viral infections can account for exacerbations in up to one-third of patients (Mohan, 2010). A range of respiratory viruses are linked to COPD exacerbations. The most common viruses associated with exacerbations of COPD are rhinoviruses, but in more severe exacerbations requiring hospitalization, influenza is more common (Seemungal, 2001; Rohde, 2003; Greenberg, 2000).

Air pollution can trigger exacerbations in patients with COPD (Ling, 2009). In up to 30% of patients with an acute exacerbation, no particular etiology is identified (Sapey, 2006). Recent evidence suggests that pulmonary embolism (PE) might account for a significant proportion of these exacerbations. A single center prospective cohort

### Table 17.1: Factors predicting an increased risk of exacerbations in patients with COPD.

1. History of prior exacerbations

2. Disease Characteristics:
   - Worsening underlying disease based on FEV₁ impairment & GOLD classification
   - Chronic cough and sputum production
   - Prednisone and/or theophylline use at baseline

3. Presence of comorbidities:
   - Gastroesophageal reflux disease
   - Pre-existing cardiovascular comorbidities
   - Poor quality of life at baseline

4. Laboratory characteristics:
   - Elevated white blood cell count
   - Elevated fibrinogen levels
   - Elevated levels of C-reactive protein
study found that in patients requiring hospitalization secondary to a severe COPD exacerbation, PE was identified in 25% cases (Tillie-Leblond, 2006). These results were further supported by a meta-analysis (Rizkallah, 2009).

17.5 Triage to Home Versus Hospital for Management of Exacerbations

The assessment of a patient with COPD exacerbation begins with a complete medical history and physical examination. It is important to have a broad initial set of differential diagnoses when evaluating a patient with COPD presenting with worsening dyspnea. Alternate diagnoses to consider include congestive heart failure, pulmonary thromboembolism, pneumonia, pneumothorax and worsening anemia. Zvezdin et al (Zvezdin, 2009) reviewed the medical records of 43 patients who died within 24 hours of admission for an acute exacerbation of COPD. The primary cause of death was heart failure (37%), pneumonia (28%), and pulmonary thromboembolism (21%); respiratory failure due to COPD progression occurred in only 14% of the patients (Zvezdin, 2009).

The medical history should include an assessment of COPD severity (usually based upon prior spirometry measuring the FEV₁ % predicted), presence/worsening of new/existing symptoms, and their comorbidities. Physical examination should focus on identifying signs which might suggest acute decompensation, such as the use of accessory muscles of respiration, paradoxical movement of the chest and abdomen, development of cyanosis, peripheral edema, change in mental status, and hemodynamic instability. In addition, the following tests may be of additional value to assess severity of the exacerbation and exclude alternate diagnoses:

1. Pulse oximetry and arterial blood gas measurement to analyze oxygenation and acid-base status
2. Chest radiographs are especially useful as they can help exclude alternate diagnoses such as heart failure, pneumonia, and pneumothorax. A clear chest radiograph might provide a clue to the presence of pulmonary thromboembolism, especially if the dyspnea and hypoxemia seem out of proportion to the degree of cough/sputum production.

3. Electrocardiogram to diagnose arrhythmias or cardiac ischemia.

4. Complete blood count to look for polycythemia, leukocytosis, thrombocytopenia or anemia.

5. Metabolic panel to evaluate electrolytes and blood sugar.

The first question to answer in the management of COPD exacerbations is to determine whether the patient needs hospitalization or can they be safely managed at home. Over 80% of exacerbations can be safely managed at home with antibiotics, corticosteroids, and bronchodilators (Hurst, 2010; Tashkin, 2008). Intensive home care or “Hospital at home” programs for management of COPD exacerbations deliver similar clinical outcomes compared with hospitalization but provide substantial financial savings (Ram, 2004). However, such an approach requires a dedicated support team and resources which are not widely available at the current time.

Overall, there is a paucity of literature when it comes to guidance in making the decision to hospitalize a patient with an acute exacerbation of COPD. To some extent this decision has to be individualized based on the available hospital and community resources. In general, criteria that might trigger hospitalization are provided by the GOLD guidelines (GOLD guidelines, 2014). These criteria can be divided into clinical, laboratory/radiologic, and psychosocial factors. Clinical examination findings such as hemodynamic instability, altered mental status, use of accessory muscles of respiration, new oxygen requirement, presence of cyanosis, severe underlying COPD, history of frequent exacerbations, failure of outpatient management, and significant comorbid conditions should prompt consideration of hospitalization. Laboratory findings such as respiratory acidosis, elevated white blood cell count, and chest radiograph showing a lobar pneumonia or significant pulmonary edema should also

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**Table 17.3: Criteria to trigger hospitalization for patients with COPD exacerbations.**

- Marked increase in intensity of symptoms, such as sudden development of resting dyspnea
- Severe underlying COPD
- Onset of new physical signs (e.g. peripheral edema, cyanosis)
- Failure of outpatient/emergency room management
- Presence of other co-morbidities (e.g. heart failure, arrhythmias)
- History of frequent exacerbations
- Older age
- Inadequate home support
- Change in mental status
prompt consideration of inpatient admission. Finally, psychosocial factors, such as older age, presence or absence of support at home, and availability of outpatient appointments for quick follow up should be evaluated prior to discharging patients from the emergency room or office.

Once a decision has been made to admit a patient with an acute exacerbation, the next step is to decide whether the patient can be safely managed on the ward or requires an ICU admission. Patients with a life threatening exacerbation should be promptly triaged to the ICU. Presence of hemodynamic instability, respiratory muscle fatigue, respiratory acidosis, persistent severe hypoxemia, need for mechanical ventilation, and altered mental status should prompt admission to the ICU. Table 17.4 summarizes the indications that warrant ICU admission for patients with an acute exacerbation of COPD. Patients not meeting these indications can generally be safely triaged to the wards. Patients with a mild exacerbation and good social support at home can be admitted under observation (less than 48 hour hospital stay) with a plan to complete the remainder of their therapy at home. This decision can be further guided by the emergency department course of these patients. Patients who start to show improvement in their symptoms in the emergency department after a few hours of treatment can generally be safely admitted for observation. However, patients with more severe exacerbations, especially patients with severe underlying disease, history of frequent exacerbations, and presence of significant cardiovascular comorbidities should be admitted to the inpatient setting with a plan to monitor them for a few days until they start to show signs of clinical improvement/stabilization.

Table 17.4: Indications for ICU admission for patients with acute exacerbations of COPD

- Changes in mental status
- Persistent and/or worsening hypoxemia (pO₂ < 40 mmHg) despite supplemental oxygen
- Presence of respiratory acidosis
- Hemodynamic instability
- Need for mechanical ventilation

17.6 Hospital Management of COPD Exacerbations

The major components of management in COPD exacerbations include reversal of airflow obstruction with short acting bronchodilators and systemic glucocorticoids, identifying and treating the trigger(s) of the exacerbation, especially treating infectious processes with antibiotics, and ensuring adequate oxygenation. In the following sections we will cover the pharmacologic management of COPD exacerbations, followed by the role of mechanical ventilation in the management of COPD exacerbations.
17.6.1 Pharmacologic Therapies for the Management of COPD Exacerbations

17.6.1.1 Supplemental Oxygen

Supplemental oxygen is a key therapy for management of COPD exacerbations. However, the use of supplemental oxygen should be judicious. Administration of high flow oxygen can lead to worsening hypercapnia and worse outcomes. The exact mechanisms for worsening hypercapnia after administration of supplemental oxygen are not clear, but likely include a combination of the following factors:

1. Worsened ventilation-perfusion matching due to attenuation of hypoxic pulmonary vasoconstriction (Aubier, 1980).
2. Haldane effect – release of carbon dioxide bound to hemoglobin due to rightward displacement of CO2-hemoglobin dissociation curve in the presence of increased oxygen saturation (Christiansen, 1914).
3. Decreased minute ventilation (Robinson, 2000).

In a prospective, randomized trial, paramedics treating patients with COPD exacerbations provided either high flow oxygen irrespective of the patient’s pulse oximeter saturations (SpO₂) or supplemental oxygen titrated to achieve SpO₂ between 88 – 92%. The mortality rate in the high flow oxygen group was 9% whereas mortality rate in the oxygen titration group was 4%. Thus, in patients with an acute exacerbation of COPD, using supplemental oxygen titrated to maintain SpO₂ between 88 – 92% reduced mortality by 58% compared with unconstrained high flow oxygen (Austin, 2010). This trial forms the basis of our recommendation to titrate supplemental oxygen to a SpO₂ of 88 – 92% in patients with COPD exacerbations.

17.6.1.2 β Adrenergic Agonists

Inhaled short acting β-adrenergic agonists (albuterol, levalbuterol) are the mainstays of pharmacological management to reverse air flow obstruction. They can be administered via a metered dose inhaler (MDI) with/without a spacer or via nebulization. Current evidence suggests that both approaches (nebulization versus MDI) are equivalent in terms of drug delivery and treatment of bronchospasm (Turner, 1997). Despite this evidence of clinical equivalency and increased cost, clinicians tend to prefer nebulized therapy on the pretext of a more uniform/reliable drug delivery.

Typical doses of albuterol are 2.5 mg by nebulizer every one to four hours as needed, or four to eight puffs (90 mcg per puff) by MDI with a spacer every one to four hours as needed. Increasing the dose of nebulized albuterol to 5 mg or using continuous nebulized β-agonists does not have a significant impact on spirometry or clinical outcomes (Nair, 2005), but might lead to increased adverse effects such as tachycardia, tremors, and hypokalemia.

Patients with severe COPD are at higher risk of hypercapnia with supplemental oxygen (discussed in the section above). This phenomenon has been observed with
the use of oxygen-driven nebulizers (Edwards, 2012). Thus, bronchodilators to be administered via nebulization should be given via compressed air nebulization rather than oxygen driven nebulization (O’Driscoll, 2008).

**17.6.1.3 Anticholinergic Agents**

Short acting inhaled anticholinergic agents (ipratropium) are commonly employed in conjunction with β-adrenergic agonists for treatment of COPD exacerbations. The typical dose for ipratropium in this setting is 500 mcg by nebulizer every four – six hours as needed. Alternatively, two to four puffs (18 mcg per puff) can be administered by MDI with a spacer every four – six hours as needed.

The evidence for this practice is conflicting. There are studies showing an additive bronchodilator effect by adding short acting anticholinergics to inhaled β-agonists (O’Driscoll, 1989). However, there is contrasting evidence that showed no additive bronchodilation was observed with the addition of inhaled anticholinergics to β-agonists (McCory, 2002).

We recommend giving a trial of inhaled anticholinergics in conjunction with β-agonists to see if patients derive symptomatic benefit. However, in the absence of robust clinical evidence behind this practice, caution should be exercised in administering anticholinergics to elderly patients with a history of benign prostatic hyperplasia. They should not be given any more frequently than every 4 hours in order to prevent anticholinergic side effects.

**17.6.1.4 Glucocorticoids**

Systemic corticosteroids, when given in conjunction with bronchodilators, can improve symptoms and shorten the hospital length of stay for patients with an acute exacerbation of COPD (Niewoehner, 1999; Quon, 2008). Corticosteroids have a nearly 100% oral bioavailability and, thus, should be administered orally unless patients are unable to take oral medications (e.g. intubated and mechanically ventilated patients). De Jong et al (de Jong, 2007) compared intravenous prednisone to oral prednisone in patients admitted with COPD exacerbation and found no difference in the rates of treatment failure, spirometric and quality of life improvement, and length of hospital stay.

The optimal dose and duration of corticosteroids for treatment of COPD exacerbations has been a subject of debate for the past few years. De Jong et al (de Jong, 2007) and Lindenauer et al (Lindenauer, 2010) compared low dose oral prednisone to high dose intravenous prednisone and found similar outcomes. Niewoehner et al (Niewoehner, 1999) conducted a double blind, randomized trial comparing a 2 week with an 8 week course of steroids for COPD exacerbations. They found that a 2 week course of steroids was similar in efficacy and outcomes to an 8 week course. This trial formed the basis for the standard 14 day steroid course for COPD exacerbations over the past decade. More recently, the 14 day steroid course was compared with a 5 day
course and the authors found similar outcomes and less corticosteroid exposure from a 5 day steroid course (REDUCE trial) (Leuppi, 2013). The dose of prednisone used in the REDUCE trial was 40 mg prednisone daily. Nebulised budesonide alone may be an alternative to systemic corticosteroids in the management of hospitalized patients with acute exacerbations of COPD (Maltais, 2002; Gunen, 2007).

Tapering of systemic corticosteroids, although a common practice, is unnecessary in most circumstances. The risk of hypothalamic-pituitary-adrenal-axis suppression is negligible when low dose, short duration corticosteroid regimens are used. No evidence exists to suggest that abruptly stopping a low-dose steroid regimen will increase the risk of disease relapse. In addition, patients find tapered regimens confusing which commonly leads to incorrect dosing (Vondracek, 2006). We recommend not initiating a tapering course of steroids unless the duration of treatment will exceed 14 days.

In summary, the trend in corticosteroid dosing is shifting to a paradigm of low to moderate doses given for a relatively short duration. Based upon the findings from the REDUCE trial (Leuppi, 2013) and the GOLD guidelines (GOLD guidelines, 2014), oral 40 mg prednisone daily for 5 days should suffice for most patients with acute exacerbations of COPD.

17.6.1.5 Antibiotics
While the utility of antibiotics is less established for mild exacerbations managed in the outpatient setting, the role of antibiotics is more established in moderate-severe exacerbations requiring hospitalization. Anthonisen (Anthonisen, 1987) compared antibiotic administration with placebo in patients with acute exacerbations of COPD and found a higher treatment success rate in patients who received antibiotics with no increase in adverse effects. Nouira et al (Nouira, 2001) compared oral ofloxacin to placebo in mechanically ventilated patients with COPD exacerbation and showed that the combined frequency of death and need for additional antibiotics, as well as duration of hospital stay and mechanical ventilation were lower in the group treated with ofloxacin. Similar improvements in outcomes after administration of antibiotics have been reported by multiple other studies (Roede, 2009; Rothberg, 2010; Daniels, 2010; and Stefan, 2013). Vollenweider et al (Vollenweider, 2012) conducted a meta-analysis of all randomized control studies on this subject and found high quality evidence supporting the role of antibiotics in the management of severe COPD exacerbations requiring hospitalization, especially patients admitted to the ICU or requiring mechanical ventilation. Similar benefit was not found in cases of mild exacerbations managed in the outpatient setting.

Based upon the above data, the GOLD guidelines recommend antibiotic administration to patients with COPD exacerbations requiring mechanical ventilation (invasive or non-invasive) or patients with increased sputum volume or purulence (GOLD guidelines, 2014). The recommended length of therapy is 5 days for most patients.
Falagas et al (Falagas, 2008) performed a meta-analysis comparing short duration antibiotic courses (5 days) with longer duration courses (7 – 10 days) and found similar treatment success rates in both groups. Additionally, patients treated with a shorter course of antibiotics had fewer adverse events.

The optimal choice of antibiotic for use in COPD exacerbations is not well established, and to some extent is dependent upon the local bacterial resistance pattern. Usual first line therapy should target the common bacterial pathogens (*Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae*) and consists of a macrolide antibiotic, penicillin, or doxycycline (Dimopoulos, 2007). In patients with severe disease, history of frequent exacerbations and/or history of exacerbation requiring mechanical ventilation, consideration must be given to the possibility of resistant organisms such as *Pseudomonas* species which will not be adequately covered by the above antibiotics. Cultures from sputum and/or lung should be performed in these high risk patients and broad spectrum antibiotics administered with a plan to de-escalate based upon the culture and susceptibility results (Soler, 1998; Miravitlles, 1999).

Measurement of serum procalcitonin should be considered in patients with acute exacerbations of COPD. Serum procalcitonin is elevated in response to bacterial infections and thus can be a useful biomarker to help decide initiation/duration of antibiotics. A recent Cochrane analysis found that use of serum procalcitonin measurement in cases of respiratory tract infections (including COPD exacerbations) did not affect mortality or treatment failure but led to a significant reduction in antibiotic exposure (Schuetz, 2012). This practice could reduce the overall cost of treatment, prevent unnecessary adverse events associated with exposure to antibiotics and also prevent emergence of resistant organisms.

### 17.6.1.6 Other Therapies

Adjuvant therapies in addition to the above measures that might benefit a hospitalized patient with an acute exacerbation of COPD include the following:

1. **Smoking cessation**: Hospitalization provides a great opportunity to get patients to quit smoking. The admission itself can act as a strong deterrent against continued active smoking (Rigotti, 2008; Keenan, 2009). Intensive counseling for smoking cessation during hospitalization (at least one contact during the hospital stay with continued support for at least one month after discharge) increased the likelihood of smoking cessation (relative risk (RR) 1.37, 95% confidence interval (CI) 1.27–1.48) (Rigotti, 2012). Addition of nicotine replacement therapy to the counselling can further increase the rates of smoking cessation (RR 1.54, 95% CI 1.34–1.79) (Rigotti, 2012).

2. **Thromboprophylaxis**: PE accounts for a significant proportion of acute exacerbations of COPD. As discussed earlier in this chapter, PE is the trigger for up to a quarter of COPD exacerbations in patients without an identified exacerbation
cause or in patients with non-resolving symptoms (Tillie-Leblond, 2006; Rizkallah, 2009). Additionally patients with COPD are at increased risk for development of venous thromboembolism and PE (Bertoletti, 2012). Adequate pharmacologic measures should be taken to prevent this complication in hospitalized patients (Kahn, 2012). Physicians should maintain a high index of suspicion to look for a deep vein thrombosis (DVT) or PE in cases of COPD exacerbations.

3. **Nutritional support**: Patients with an acute exacerbation of COPD tend to have negative nitrogen balance and use of nutritional supplements to target a daily caloric intake of 1.5 times their resting energy expenditure leads to modest improvements in lung function and general well-being scores (Saudny-Unterberger, 1997).

4. **Management of comorbidities**: COPD coexists with multiple other comorbidities which can negatively affect patients’ prognosis (Barnes, 2009). Cardiovascular disease is the most frequent comorbidity in patients with COPD and frequently complicates the hospital course and management of patients admitted with a COPD exacerbation (Almagro, 2012). The major cardiovascular comorbidities coexisting with COPD include hypertension, ischemic heart disease (IHD), heart failure (CHF), and atrial fibrillation (Almagro, 2012). Distinction between heart failure and COPD exacerbation can sometimes be difficult based on history, and further investigations such as chest radiographs, serum brain natriuretic peptide (BNP), and echocardiography may be helpful in distinguishing the two conditions. In general, these comorbidities should be managed according to their respective guidelines, as there is no evidence to suggest that these manifestations should be treated differently in the presence of COPD (GOLD guidelines, 2014).

   There is an increased risk of myocardial ischemia in patients admitted with acute exacerbations of COPD (Donaldson, 2010). The biggest management conundrum in the presence of combined COPD and cardiovascular disease is the ability to use β-blockers. β-blockers have a significant mortality benefit in cases of ischemic heart disease and congestive heart failure (Hunt SA, 2009; Kushner FG, 2009), and are under-utilized because of concern for worsening bronchospasm (Stefan, 2012). Multiple studies have shown that selective β₁-blockers can be safely administered to patients with COPD (Stefan, 2012; Salpeter, 2005). In a cohort study of patients with COPD, Quint et al (Quint, 2013) found that use of β-blockers either started at presentation for MI or continuation of previously prescribed β-blockers was associated with a reduction in mortality. Thus, the benefits of β-adrenergic blockade in cases of IHD or CHF far outweigh any concerns for worsening bronchospasm and should not be withheld from patients with COPD exacerbations.

5. **Other therapies** such as mucolytic agents e.g. N-acetylcysteine, methylxanthines e.g. theophylline and aminophylline, and chest physiotherapy have not been shown to be beneficial in management of COPD exacerbations, and, thus, should not be routinely used for these patients (Black, 2004; Snow, 2001).
17.6.2 Mechanical Ventilation for Acute Exacerbations of COPD

17.6.2.1 Noninvasive Positive Pressure Ventilation (NIPPV):
NIPPV refers to positive pressure ventilation delivered via a noninvasive interface (nasal mask, oral mask or nasal prongs) as opposed to an invasive interface (endotracheal tube, tracheostomy). The use of NIPPV is becoming more common as we realize the benefits offered by this modality compared to invasive mechanical ventilation.

Perhaps, the best studied use of NIPPV has been in cases of hypoxemic and hypercapnic respiratory failure from COPD exacerbations. NIPPV reduces arterial carbon dioxide levels, corrects acidosis, decreases work of breathing, decreases hospital length of stay, and avoids complications of mechanical ventilation such as ventilator associated pneumonia. More importantly, use of NIPPV improves overall survival compared with invasive mechanical ventilation (Brochard, 1995; Plant, 2000; Chandra, 2012; Ram, 2004; Conti, 2002). In a meta-analysis by Ram et al (Ram, 2004), the use of NIPPV for COPD exacerbations was associated with almost 50% reduction in mortality (11% versus 21%). Thus, NIPPV is probably the treatment modality offering the largest mortality benefit in cases of acute exacerbations of COPD.

An oronasal mask might confer the most physiologic advantage in these patients (Navalesi, 2000) but, in reality, the choice of mask is more dependent upon patient comfort. A starting inspiratory pressure (IPAP) of 8–12cms H2O, and an end expiratory pressure (EPAP) of 4–6 cms H2O is a reasonable start for most patients. Further titration of inspiratory and expiratory pressures is based on the clinical condition and gas exchange parameters. Patients initiated on NIPPV should be closely monitored and a repeat blood gas obtained after 1–2 hours of NIPPV. Improvement of pH and carbon dioxide within this time frame portends a good prognosis (Anton, 2000). As a corollary to this, if patients fail to show improvement/stabilization in their gas exchange parameters or clinical condition within the first two hours after initiation of NIPPV, they should be intubated and placed on invasive mechanical ventilation.

Table 17.5: Indications for initiation of Noninvasive Positive Pressure ventilation (NIPPV)

<table>
<thead>
<tr>
<th>At least one of the following:</th>
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<tbody>
<tr>
<td>- Respiratory acidosis (Arterial pH ≤ 7.35, or PaCO2 &gt; 45 mmHg)</td>
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<tr>
<td>- Severe persistent hypoxemia (Arterial PaO2 &lt; 40 mmHg)</td>
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<tr>
<td>- Severe dyspnea with clinical signs suggestive of respiratory muscle fatigue</td>
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<tr>
<td>- Increased work of breathing, as evidenced by use of accessory muscles of respiration, paradoxical motion of abdomen, or intercostal muscle retraction</td>
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Inpatient Management of Acute COPD Exacerbations

17.6.2.2 Invasive Mechanical Ventilation

Endotracheal intubation and invasive mechanical ventilation is typically reserved as the last resort in the management of COPD exacerbations, and are used when patients have either failed or not tolerated a trial of NIPPV or there are contraindications to the use of NIPPV (Table 17.6). The goals of invasive mechanical ventilation are the same as NIPPV and include reduction in work of breathing, correction of acidosis, and prevention of dynamic hyperinflation. Volume controlled modes of ventilation are most commonly used for this purpose with assist control mode (AC) being the most common mode of mechanical ventilation.

With mechanical ventilation, careful attention has to be given to avoid overventilation that can lead to air trapping and dynamic hyperinflation. Dynamic hyperinflation can lead to barotrauma and decreased venous return causing cardiovascular collapse and death (Tobin, 2001). Dynamic hyperinflation is characterized by increased levels of intrinsic positive end expiratory pressure (Auto-PEEP). Auto-PEEP is very common in patients with COPD (MacIntyre, 1997) and can lead to significantly increased work of breathing (Coussa, 1985). An indication of the presence of auto-PEEP can be the presence of one or more of the following: 1) ineffective triggering on the ventilator, 2) increasing peak pressures, 3) the beginning of inspiratory flow before expiratory flow reaches zero (Ranieri, 1995). Auto-PEEP can be quantitatively assessed by measuring the airway opening pressure during an end-expiratory pause (Pepe, 1982). The quantitative measurement might be helpful as it provides a guide to the amount of extrinsic PEEP that should be used. As a rough estimate, the applied or extrinsic PEEP should be approximately 80% of the auto-PEEP (Ranieri, 1993). Other strategies to reduce auto-PEEP include reducing the minute ventilation and prolong-

| Table 17.6: Contraindications for use of Noninvasive Positive Pressure ventilation (NIPPV) |
| At least one of the following: |
|   - Aspiration risk |
|   - Altered mental status |
|   - Hemodynamic instability |
|   - Cardiac/respiratory arrest |
|   - Severe agitation |

| Table 17.7: Indications to initiate invasive mechanical ventilation |
|   - Failure to tolerate NIPPV |
|   - Contraindications to the use of NIPPV |
|   - Failure to improve gas exchange parameters after trial of NIPPV (2 hours) |
|   - Massive aspiration |
|   - Inability to handle respiratory secretions |
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Close attention must be paid to the size of the endotracheal tube in mechanically ventilated patients with COPD. Whenever possible, avoid smaller diameter endotracheal tubes as increased resistance through the smaller tube can contribute to Auto-PEEP. Occasionally, patients can present with severe Auto-PEEP causing decreased venous return and cardiovascular collapse. Immediate, short duration disconnection from the ventilator (to allow “deflation” and reduction in hyperinflation) can be a lifesaving maneuver in this circumstance. Mechanical ventilation can then be resumed with reductions in minute ventilation and the addition of extrinsic PEEP.

COPD exacerbations that require mechanical ventilation are associated with worse outcomes and increased mortality (Seneff, 1995). Thus, every effort should be made to identify the patient’s wishes (advance directives or living will) prior to initiating mechanical ventilation.

Weaning from mechanical ventilation can be difficult in patients with COPD. The major determinant in a patient’s ability to be liberated from the ventilator is the

<table>
<thead>
<tr>
<th>Table 17.8: Summary of management of hospitalized patients with an acute exacerbation of COPD.</th>
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<tbody>
<tr>
<td><strong>Diagnostic testing</strong></td>
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<tr>
<td>- Assess oxygen saturation with pulse oximetry</td>
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<tr>
<td>- Routine labs such as CBC, Renal panel</td>
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<tr>
<td>- Chest x-ray to assess for pneumonia, heart failure, pneumothorax etc</td>
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<tr>
<td>- Arterial blood gas in severe exacerbations or patient exhibiting signs of respiratory distress</td>
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<tr>
<td><strong>Supplemental oxygen:</strong> Titrate to keep oxygen saturation between 88 – 92%</td>
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<tr>
<td><strong>Inhalers:</strong></td>
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<tr>
<td>- β-adrenergic agonists (Albuterol) and anticholinergic agents (Ipratropium).</td>
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<tr>
<td>- Avoid aggressive use of anticholinergic agents to prevent side effects especially in elderly patients.</td>
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<tr>
<td>- Use compressed air nebulizers rather than oxygen driven nebulizers</td>
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<tr>
<td><strong>Glucocorticoids:</strong></td>
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<tr>
<td>- Moderate dose glucocorticoids are as effective as high dose.</td>
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<tr>
<td>- Oral steroids have similar efficacy to intravenous steroids</td>
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<tr>
<td><strong>Antibiotics:</strong></td>
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<tr>
<td>- Macrolide, or respiratory fluoroquinolone as first line agents</td>
</tr>
<tr>
<td>- May have to alter antibiotic choice based on likely pathogens and local antibiograms</td>
</tr>
<tr>
<td><strong>Mechanical Ventilation:</strong></td>
</tr>
<tr>
<td>- Noninvasive positive pressure ventilation (NIPPV), is the preferred mode of mechanical ventilation, unless absolute contraindications exist</td>
</tr>
<tr>
<td>- Consider for patients with respiratory acidosis, hypoxemia, or signs of respiratory distress/ fatigue</td>
</tr>
<tr>
<td>- Close monitoring to assess for need of invasive mechanical ventilation</td>
</tr>
<tr>
<td>- Use NIPPV to assist with weaning from invasive mechanical ventilation</td>
</tr>
</tbody>
</table>
ability of the respiratory muscles to cope with the ventilatory load (Purro, 2000). Use of NIPPV to facilitate weaning can significantly improve the chances of successful extubation (Nava, 1998). In addition, early use of NIPPV in patients with hypercapnia following a spontaneous breathing trial reduced the risk of respiratory failure and improved 90 day mortality (Ferrer, 2009).

### 17.7 Hospital Discharge and Follow up

The optimal duration of inpatient stay for management of COPD exacerbations is unclear. Length of stay of 6–7 days has been quoted based on the results by Mushlin et al (Mushlin, 1991). However, in today’s age, with better organized transitions of care between inpatient and outpatient teams, the optimal length of stay is likely shorter for most patients. A patient’s home medications should be initiated prior to discharge to ensure efficacy of the regimen. It might be prudent to continue inhaled corticosteroids even in the presence of systemic steroids, in order to emphasize adherence and ensure continuity of the home regimen after systemic steroids are discontinued. The requirement for supplemental oxygen should be addressed at rest and with exertion prior to discharge.

**Table 17.9:** Items to assess prior to discharge from hospital

- Smoking cessation
- Ensure efficacy of home inhaler regimen
- Reassess inhaler technique
- Need for supplemental oxygen, at rest and with exercise
- Adequate outpatient follow up
- Management and follow up plan for other comorbidities
- Ensure patient and/or home caregivers understand the management plan and provide written instructions for the same

The goal after hospital discharge is to prevent future exacerbations and hospitalizations. Prior hospital admissions, use of oral corticosteroids, long term oxygen use, poor health related quality of life, and lack of physical activity are associated with an increased rate of readmissions (Bahadori K, 2007). Effective communication between hospital providers, patient/family, and outpatient physicians is critical to prevent future readmissions. These patients should be reassessed 4 – 6 weeks after hospital discharge. Smoking cessation, effectiveness of the outpatient medical regimen, inhaler technique and vaccination status should be addressed during this follow up. In patients with frequent exacerbations, long term use of macrolides such as azithromycin (Albert, 2011), or phosphodiesterase inhibitors such as roflumilast (Chong, 2013) should be considered in order to reduce the frequency of exacerbations. When compared to conventional care, pulmonary rehabilitation after an acute exac-
Acute exacerbations of COPD are a leading cause of morbidity and mortality worldwide. The majority of these exacerbations can be successfully treated in the outpatient setting; however, severe cases require hospitalization. Detailed investigations to determine etiology of exacerbations as well as management of underlying comorbidities is essential for successful management of these patients. Careful attention must be paid to the presenting symptoms and underlying comorbidities in order to properly triage these patients from the emergency room. The use of NIPPV has led to significant reduction in mortality from acute exacerbations of COPD. Effective communication between inpatient providers, patients, families and primary care providers is essential in order to prevent recurrent hospitalizations from COPD exacerbations.

17.9 Summary Points

1. Acute exacerbations of COPD are significant contributing factors to the morbidity and mortality burden of COPD.
2. The distinction between COPD exacerbations and underlying cardiovascular comorbidities can be difficult but must be done promptly as it can have a significant impact on management and subsequent mortality.
3. History of frequent exacerbations, severity of underlying disease, and the presence of significant cardiovascular comorbidities are the main factors predicting future exacerbations as well as increased risk of hospitalization.
4. Avoid excessive use of anticholinergic inhalers in order to prevent adverse effects, especially in elderly patients.
5. Administration of β-blockers is safe in patients with COPD and should not be withheld, especially in patients with significant cardiac history.
6. Early use of NIPPV should be considered in severe exacerbations for initial mechanical ventilator support as well as to facilitate weaning and liberation from invasive mechanical ventilation.
References


18 Primary Care and Interaction with Specialty Care for the COPD Patient

Key Points
1. The Primary Care team will ultimately manage the care of the patient with COPD in close collaboration with Pulmonary Services.
2. Relationships between Primary Care and Pulmonary Specialists must be collaborative, fluid, and respectfully recognize each provider’s unique role in the care of the patient.
3. Traditional management of the COPD patient in the primary arena setting has changed and includes expanding roles and responsibilities of all team members.

18.1 Introduction: A Healthcare System in Crisis and New Models of Care

The U.S. Healthcare System continues to face a challenging environment including rising healthcare costs while achieving mediocre health outcomes for its population of 311 million people. The current healthcare system is saturated with inconsistent coordination and discontinuous care, poor access to both Primary Care and Specialty Services (Pulmonary; Cardiology) and increasing numbers of emergency room visits, hospitalizations and hospital readmissions (Ewing, 2013). In addition, the US spends approximately $3.6 trillion dollars per year on healthcare which is an average of over $8000.00 per citizen. In addition, the US population is living longer with an average life expectancy of 82.2 years for women and 77.4 years for men. With this aging population, the process of chronic disease management becomes critical in the Primary Care setting (Wat, 2014). The percentage of Americans struggling with a chronic disease such as cardiac disease, diabetes, hypertension, chronic obstructive pulmonary disease, obesity and cancer is staggering and affects at least 133 million adults which is nearly one in two adults. Seven percent of U.S. children also suffer from at least one chronic disease including diabetes, hypertension, and obesity. The consequences of these chronic disorders are sobering; 70% of all adult deaths are attributed to chronic diseases and more than 75% of the U.S. health care budget is spent on the management of chronic disease (Richmann, 2014). These results have stimulated the examination and testing of other models of providing and managing Primary Care to the U.S. population. One proposed solution is a redesign of the primary care outpatient setting called the Patient Centered Medical Home (Higgins, 2013).
The Patient Centered Family Medical Home Model

The Patient Centered Care Medical Home Model is a patient driven, team based approach that delivers efficient, comprehensive, and continuous care through active communication and coordination of healthcare services (Daschle, 2013). It is based on a set of seven principles: 1) respect for the patient; 2) coordination and integration of care; 3) emphasis on communication and education between the patient and staff; 4) emphasis on physical comfort; 5) emotional support/alleviation of fear and anxiety; 6) involvement of family and friends and 7) attention to transition and continuity of care and improved access (Jackson, 2013). The Patient Centered Care Medical Home Model is also known by a variety of other names such as the Patient Aligned Care Team or PACT (Veterans Administration System). This team structure has the patient at the center of the process and dictates that the patient is no longer the passive recipient of healthcare but rather is viewed as an integral and active participant. In fact, the patient is recognized as the most important member of the health care team. Thus, the patient and provider are reconfigured into a shared decision making model where the patient ultimately will decide on the unique plan of his/her care. The matriarchal/patriarchal all-knowing physician is no longer viewed as the epitome of medical care. Surrounding that unique patient are the members of the Primary Care Team consisting of a Primary Care Provider (medical doctor, nurse practitioner or physician assistant), registered nurse, licensed practical nurse and medical support assistant. In addition, integrated into the Primary Care Team are allied health providers including nutrition, pharmacy, social work, and mental health (Yoon, 2013). (Figure 18.1).

**Figure 18.1:** Organization of the Patient Aligned Care Team (VA Team Training, 2014)
To complicate improvement in primary care further, the U.S. continues to face a growing need for primary care physicians and will need an additional 52,000 doctors by 2025. The reasons for the primary care physician shortage are complex and include population growth, an aging population, the rising cost of medical school, more lucrative specialty care opportunities, and scope of practice laws. There is projected to be a substantial shortage of non-primary care specialists of 33,100 in specialties such as cardiology, oncology, and emergency medicine. Thus, other providers such as nurse practitioners and physician assistants are helping to fill the gap in care. In addition, other allied health providers such as nutritionists, pharmacists, mental health providers, and physical therapists are being relied upon more frequently to help in the management of chronic disease and lifestyle issues (Herman, 2014).

Specialty care is viewed as a secondary tier and to be consulted only when primary care has a question or problem with a complex patient. In this model, only the most complex and sickest patients are seen by specialty care. This practice redesign creates improved access for specialty care; however, it conversely increases the workload for the primary care team. It is expected that the primary care team will manage most of the care of the patient including specialty services. This assumes that the primary care team has additional skills, experience and professional development to feel comfortable in managing the complex specialty patient (Pagan, 2013).

18.3 How Does the PACT Team Differ from Traditional Roles/Responsibilities?

The Family Medical Home or Patient Aligned Care Team must have an organizational foundation of patient centeredness, continuous improvement, and adequate resources. The very structure of the team is built on patient access, care management, and coordination and practice redesign. Patient access to the team is a cornerstone of practice; however, the traditional face-to-face provider patient visit is rapidly being reconstructed to include non-traditional visits such as scheduled telephone visits when a physical exam is not needed, secure messaging (email), and group medical appointments for chronic disease management. The patient is typically seen on an annual basis for a wellness exam and certainly for ill visits when a physical exam is imperative. Thus, the non-traditional visits allow improved access via alternative pathways for patients to interact with their family medical home. In addition, other allied professionals including nutrition, social work, mental health, pharmacy and, in some settings, substance abuse, chronic disease case management (COPD/Diabetes), and physical therapy are relied upon for their expertise. These professionals are integrated directly into the teams. In this way, patients are able to access a variety of professionals at point of care in the primary care setting as a formalized appointment or as a “warm handoff” (Roseland, 2013).
How Does the PACT Team Differ from Traditional Roles/Responsibilities?

Patient care management and coordination are key to the family medical home. In particular, the team identifies those patients who are at higher risk for emergency room visits and inpatient hospitalizations due to their complex medical and psychological histories. Chronically ill patients (COPD, diabetes, coronary artery disease) are followed more closely utilizing non-traditional visits with the team nurses and allied health professionals. Team care is focused on prevention, management of chronic disease, and coordinating transitions of care. In particular, continuity of care can be challenging when patients are seen by specialty care, in the emergency room and/or admitted and discharged from inpatient hospital stays. The problems most commonly encountered include discrepancies in medication management, failure to understand medications, and overall lack of understanding in the plan of care. This is true not only for the patient but often for the primary care team and creates tension often between services. Primary care often feels as if they are responsible for coordinating the care for a patient with limited communication from specialty care (Plaisance, 2010; Kilo, 2010; Gardner, 2014).

Finally practice redesign has been instrumental in the reconfiguration of how primary care is provided to the patient. The family medical home has expanded the roles, responsibilities, and tasks of each member of the team. Each team member is encouraged to practice at the top of their educational level (Swartwout, 2014). This team approach enables its members to value each member’s skills and expertise, thereby promoting communication and teamwork. Frequently teams have designated weekly meetings to discuss high risk patients and management strategies. During these team meetings, workload dealing with both patient visits and non-visit work such as paperwork for family medical leave is discussed and distributed as dictated by time, skill level, educational competencies, and training. In this way, all visit and non-visit work is distributed amongst the team members, freeing up the provider to focus on patient management (Coulmont, 2013). (Figure 18.2)
18.4 General Roles of the PACT Team

The patient centered primary care team includes the patient, clerical associate, clinical associate, nurse care manager and the provider. Each team member is responsible for a specific function within the PACT. The patient is central to the entire team and has the responsibility to schedule appointments as needed, participate in face to face visits, prepare for primary care visits, and participate in all care. The clerical associate specializes in customer service, team work, and clerical office support. Direct patient care, secure messaging, care management, teamwork, patient education and clinical support are the duties of a PACT clinical associate. The nurse care manager anchors the team with a multitude of duties including: direct patient care, group visits, patient/family education, disease management, daily huddles, team meetings, health education, and patient coaching. Finally, the provider focuses on the management of complex patients through direct patient care, group visits, telephone visits, and secure messaging (Maeng, 2013; Hoff, 2013; Baxter, 2013).

18.5 Care Management of the COPD Patient PACT Roles and Responsibilities

Comprehensive care management of the total patient is the cornerstone of PACT team practice. Importantly, the patient is at the center of the structure of his/her management. For a patient with COPD, this structure becomes even more critical to optimize pulmonary health and prevent further disease progression. Surrounding that structure are the tools necessary to help the patient maintain optimal health including: personalized health care planning, labs/imaging studies, medication reconciliation, preventive services, protocols, consults, referrals, and local community resources (Comlossy, 2012).

18.5.1 The Patient

First and foremost, the patient is involved at the very beginning of his/her primary care visit and plan of specialty care. This model dictates that the patient is responsible for scheduling appointments, preparing for appointments, and participating in his/her unique plan of care. The personalized health plan (PHP) is a tool used to individualize the care provided by the team for that patient. It is patient driven, holistic in approach, and offers the patient a choice of what area of their health care they would like to improve. There are a variety of models but they all center around the broader questions of why health is important to the patient and the patient’s selection of the primary health focus. The tools present areas of health assessment and prevention such as: be tobacco free, eat wisely, be physically active, limit alcohol, feel spiritu-
ally connected, manage stress, and be involved in one’s healthcare. Thus, the patient chooses their area of focus and the team becomes more of a coach to help that patient achieve their self-determined goal. This approach is a fundamental change in how healthcare is now being delivered in the United States. Historically, it was the provider (almost always a physician) who dictated to the patient the plan of care. There was almost always no negotiation, limited discussion, and minimal education given to the patient. Now the patient has become the central player in the delivery of his/her own healthcare and as such the process has become more equalized and a more shared decision making process (Jarousse, 2013; Berryman, 2013). For the patient with COPD, the PHP can focus on tobacco cessation, medication review, proper use of inhalers and participation in pulmonary rehabilitation. The plan may also focus on a mental health issues common to COPD patients such as depression or anxiety.

Laboratory and imaging studies are important diagnostic tools used to diagnose and treat illness. In this model, the patient is able to obtain his/her results by accessing a secure website which includes all the components of the patients’ electronic medical chart or EMC. In this way, the patient again has access to critical data in the individualized plan of care (Jampel, 2013; Mancuso, 2013).

18.5.2 Clerical Associate (CA)

This member of the team is the first line of contact with the patient and the very face of the PACT Team. As such, all initial communication relating to patient visits and concerns are triaged through this team member including such things as scheduling, reminder calls, managing sick and informational calls to the team, obtaining outside records, faxing information back to outside facilities, and issues with customer service. Clerical associates are experts in day to day mechanics of running an outpatient office. For the COPD patient, the clerical associate will need a basic understanding of the disease so that when a patient calls, the clerical associate can assist in triaging the severity of the patient’s symptoms and can schedule an emergent ill visit with a provider or other appropriate healthcare visit. Integral to the management of a specialty patient, any recent change in care such as an inpatient stay or change in medication will need to be verified though acquirement of records (McNellis, 2013).

18.5.3 The Clinical Associate

The clinical associate is the first clinical person to assess the patient after they are checked into the PACT Team. As such, the associate performs the initial assessment of the patient including collection of data related to the visit, vital signs, prevention screening, and administration of immunizations, medications, and treatments. This team member is the initial responder to triaged messages (secure messaging) as well
as telephone messages related to clinical concerns. It is often this team member who reminds the provider that the patient with COPD requires immunizations such as influenza and pneumonia vaccinations. The clinical associate is also trained to do point of care screening with spirometry for the patient suspected of having a pulmonary disorder. This clinical member is often the educator and instructs the patient on the use of his/her inhalers and the use of a spacer. The personalized health care plan for the COPD patient is often started by the clinical associate. Often this clinical member is the first to initiate treatment or other medications promptly (True, 2013).

### 18.5.4 Nurse Case Manager

This professional registered nurse anchors the team and provides direct patient care, triaging and clinically responding to secure messaging, phone calls and walk-in ill visits. The nurse is responsible for assisting with chronic disease management, coordinating transitions of care, and daily team work.

This team member is an expert in medication reconciliation which is especially important for the patient with COPD. Medication reconciliation continues to be one of the most important tasks for both the team and patient and it may be extremely time consuming to perform medication reconciliation correctly. Often medications are changed during a specialty visit or inpatient hospital stay and poorly communicated to both the patient and the PACT. The nurse case manager is an expert educator and reviews each medication with the patient including its purpose and how and when it is to be administered. The nurse is able to assess clinically a specialty patient and determine the needs of that patient in consultation with the primary care provider. This team member has a huge role in both family and patient education, coordination of transitions of care referrals such as pulmonary rehabilitation, home care, palliative care and hospice. The care manager also has a vast knowledge of outside community resources which may be of use for a COPD patient including meals on wheels, the Council On Aging and the American Cancer Society (Worth, 2012; Lewis, 2012).

### 18.5.5 The Provider

The provider in a PACT is an expert in direct patient care. Direct patient care as redesigned in PACT includes not only traditional face-to-face visits (well and ill visits) but also non-traditional visits such as telephone visits, secure messaging, and group medical appointments. The use of alternative visits theoretically improves patients’ access to their provider and teams. Telephone visits are used when a physical exam is not necessary and the patient issue can be resolved on the telephone. Telephone visits are frequently used for a follow up from a previous visit, medication titration, discussion related to labs and imaging and plan of care. Secure messaging (by email)
is an easy way for a provider to answer a question, renew a medication, or assess a patient issue in writing. Group visits are used to educate and manage chronically ill patients with the same diagnosis. The provider’s main role is to provide care for patients through disease management of both complex and stable/chronic patients, preventative care, record review, view alerts, review of diagnostic results, referrals to specialty care, final medication reconciliation, initiation of the personalized health care plan, narcotic contracts, and referrals to additional community resources and services (Hoff, 2012; VA Teamlet training 2013).

18.6 COPD and PACT

The recognition and diagnosis of COPD are the initial steps in the provision of COPD care management. All patients with a history of tobacco use and/or environmental exposure and respiratory symptoms should be evaluated with spirometry to determine the presence of airflow limitation. Spirometry and pulmonary function tests are interpreted by specialty care; however, the interpretation and results still need to be reviewed and understood by the provider. In many cases, patients are assigned a diagnosis of COPD without adequate diagnostic testing. This leads to incorrect diagnosis and treatment. After diagnosis, the provider will need to determine what medications should be ordered for the patient based on the physical assessment and patient evaluation. The provider should be familiar with the different classes of respiratory medications such as short and long acting β adrenergic agonists and anti-cholinergics commonly used for the treatment of COPD. A basic understanding of aerosol inhalers, the use of spacers, and the ability to instruct patients how to use their inhalers correctly is critical. Other basics needed to properly assess the COPD patient are baseline studies such as chest x-rays, electrocardiogram, and annual labs. Preventative immunizations (influenza and pneumococcal vaccines) are essential. Tobacco cessation should always be discussed and assessed as stopping smoking is the single most important life change a COPD patient can make. An emergency plan is critical when exacerbations are expected and should include a treatment plan (antibiotics and steroids) and the patient must be instructed on how and when to use the emergency plan. Pulmonary rehabilitation should always be discussed with patients and they should be referred when appropriate. Medication reconciliation is imperative for both the provider and the COPD patient. Finally, it is the provider who should finish the personalized health care plan and negotiate goal setting and subsequent primary care appointments with the patient (Panos, 2013).

In conclusion, care management for the COPD patient is complex and requires a team approach to meet the patient’s needs. Several areas of management can be initiated by all clinical team members including direct patient care, medication reconciliation, required referrals, and initiation of the PHP. (Figure 18.3).
The Primary Care Provider and PACT team are the patients’ first line of entry into the health care system. The team needs to be familiar with the recognition and early diagnosis of COPD to properly manage these complex patients.

It is important to note that primary care PACTs may need extra training and education to feel comfortable when managing complex chronically ill pulmonary patients. Providers who attended a six week mini-COPD residency at the Cincinnati VA Medical center found that they were more comfortable with the COPD patient. This education provided the PACTs and the specialists time to get to know one another and to learn each other’s role in keeping the COPD patient healthy. The residency was a series of six lectures on the basics of COPD, early recognition and diagnosis, spirometry and interpretation of pulmonary function tests, medications specific to COPD and proper use of inhalers and spacers, smoking cessation, Motivational Interviewing and multiple case studies for review (Panos, 2013).

A team approach with not only the PACT but integrating the pharmacist and the social worker into the team is instrumental. In a 2013 qualitative study, COPD patients were unclear of their medications, had multiple social and mental health issues and needed extra nursing education to better manage their chronic disease (Mulhall, 2013).

Specialty care is an important piece of the COPD patient’s overall plan of care. Pulmonologists should be utilized for those complex respiratory patients who are difficult to manage. They should be used a resource service and provide expert guidance on the management of the COPD patient. A COPD nurse educator or manager of pulmonary rehabilitation may also be used by the PACT as a resource for patient education, clinical questions, and may act as a bridge to connect the inpatient and outpatient services ensuring continuity of care.
Finally, the COPD patient will typically have exacerbations and remissions of their chronic disease state and may require hospitalizations to stabilize their pulmonary status. Thus, hospitalists will be managing the patient while they are inpatients and may request input from specialty care. Again, communication is at the forefront of transitions of care and the individualized plan of care needs to be communicated back to that primary care provider and PACT (Panos, 2013). A transition of care discharge summary note to help to direct care at patient discharge should be written by the hospitalist/pulmonologist and flagged to the team. This communication ensures continuity of care and helps the team manage the COPD patient in the outpatient setting.

COPD patients are not only complex medically but often need additional support from other specialists including mental health and tobacco cessation counselors. These additional professionals can help in the management of tobacco use/abuse and mental health issues such as anxiety and depression (Bao, 2013).

In conclusion, a partnership needs to exist between the patient, the primary care PACT, the pulmonary specialist and allied health providers. Through this partnership (Figure 18.4), the patient should obtain the best care for a long, active, and meaningful life (Pourat, 2013).

### 18.7 Summary Points

1. The US health care delivery system is evolving toward a Patient Centered Family Medical Home Model.
2. Comprehensive care management focuses all team members including administrative/clerical, nursing, and provider staff on the patient and everyone functions at their maximal level.

3. Management of patients with COPD involves a cadre of primary care team members and specialists whose collaboration, integration, and communication is essential for optimal care.

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Ralph J. Panos, MD

19 Integrating Supportive, Palliative, and End of Life Care for COPD

Key Points:
1. COPD is a chronic disease with a trajectory and natural history that is poorly predicted for any individual patient.
2. The prognosis of COPD is frequently as poor as lung cancer but patients with COPD often do not have discussions about advanced care planning with their providers.
3. Because disease trajectory is not well predicted for individual patients with COPD, advanced care planning should be incorporated into chronic disease management beginning at the time of diagnosis.
4. Advanced care planning includes information about COPD, its natural history, pharmacologic and nonpharmacologic management, comorbidities, potential for exacerbations, treatments for breathlessness, anxiety, and depression, and life sustaining interventions including invasive mechanical ventilation and resuscitation.
5. Multidisciplinary teams may enhance advanced care planning.
6. Patients’ families and other caregivers should participate in advanced care planning.

19.1 Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive, incurable yet treatable disorder that is a significant cause of disability, morbidity, and mortality. COPD is one of the few chronic processes that is increasing in prevalence and is predicted to become the third leading cause of death and fourth leading cause of worldwide disability in 2020. Although new and effective treatments are now available that reduce COPD’s morbidity and mortality, there is no cure and many individuals die of or with COPD. During the course of their illness, patients with COPD frequently experience insidiously progressive breathlessness, physical and emotional deterioration, and social isolation. Advanced care planning is the process through which providers communicate with patients and their families and support networks to prepare a comprehensive COPD management strategy. Advanced care planning incorporates therapeutic, supportive, palliative, and end of life care. Therapeutic and supportive care is treatment that helps patients and their families cope with COPD and its treatment from pre-diagnosis, diagnosis, and care into chronic management, continued illness, death, and, finally, bereavement (www.endoflifecumbriaandlancashire.org.uk/info_patients_carers/definitions.php accessed 2014). (Figure 19.1)
Palliative care is an approach that improves the quality of life of patients and their families facing the problem(s) associated with life-threatening illness through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and physical, psychosocial and spiritual care. (www.who.int/cancer/palliative/definition/en/, accessed 2014) Palliative care is multidimensional and its critical elements are presented in Table 19.1.

In addition to acute management, palliative care includes enhancing quality of life, helping with medical decision making, and identifying the goals of care, addressing the needs of family and other formal and informal caregivers, and providing opportunities for personal growth (National Consensus, 2004). End-of-life care encompasses the final stage of life during the terminal phase of the disease process and provides care for the dying person and their family and support network (Curtis, 2008).
**Integrating Supportive, Palliative, and End of Life Care for COPD**

**19.3 Patient and Caregiver Burden**

COPD is a persistent, treatable yet incurable, chronic disorder that is marked by exacerbations with intensification of respiratory symptoms; in early disease, the major causes of death are cardiac and oncologic comorbidities; whereas in later disease, respiratory failure predominates (discussed in Chapter 9, Natural History, Phenotypes, and Gender Differences in COPD; and Chapter 10, COPD Is a Multi-organ Disorder: Systemic Manifestations). Patients' health and quality of life are eroded by not only the respiratory manifestations of COPD but also the associated nonpulmonary processes (discussed in Chapter 10, COPD Is a Multi-organ Disorder: Systemic Manifestations). Current pharmacologic and nonpharmacologic treatments have significantly improved respiratory symptoms, reduced the frequency and severity of exacerbations, and consequences of COPD, but, nevertheless, the decline in respiratory function progresses as patients with COPD age. Patients with COPD often note what McMillan Boyles and colleagues (McMillan Boyles, 2011) have described as the invisible disability of COPD: the disparity between their outward normal appearance and their impaired functional status. Pinnock and coworkers (Pinnock, 2011) describe COPD not as an illness but an altered way of life. As functional impairment progresses, individuals with COPD enter a downward spiral. Their increasing physical limitations prompt a more sedentary life style restricting social interactions and activities that further reduces physical conditioning and function precipitating feelings of low self worth and depression. The less they do, the less they are able to do and a downward spiral ensues. COPD is associated with ubiquitous and insidiously pervasive effects on all aspects of life (Table 19.2).

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**Table 19.1: Critical Elements of Palliative Care**

(www.who.int/cancer/palliative/definition/en/, accessed 2014)

<table>
<thead>
<tr>
<th>Essential Components of Palliative Care</th>
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<tbody>
<tr>
<td>- Provides relief from pain and other distressing symptoms;</td>
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<tr>
<td>- Affirms life and regards dying as a normal process;</td>
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<tr>
<td>- Intends neither to hasten nor postpone death;</td>
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<td>- Integrates the psychological and spiritual aspects of patient care;</td>
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<td>- Offers a support system to help patients live as actively as possible until death;</td>
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<tr>
<td>- Offers a support system to help the family cope during the patient's illness and in their own bereavement;</td>
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<tr>
<td>- Uses a team approach to address the needs of patients and their families, including bereavement counseling, if indicated;</td>
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<tr>
<td>- Will enhance quality of life and may also positively influence the course of illness;</td>
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<tr>
<td>- Is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications.</td>
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</table>
The trajectory of decline is not predictable for an individual patient with COPD. Retrospective studies of the needs of patients with COPD during the last year of life reveal that nearly all of them experienced breathlessness (98%), fatigue or weakness (96%), low mood (77%), and pain (70%) (Elkington, 2005). Symptom relief was poor with only half experiencing relief of breathlessness and 82% not receiving treatment for their mood. Many, 41%, were housebound, leaving their home once or less monthly. Patients with COPD often have a poor understanding of this disease. They may be unaware of its chronic, progressive course despite concerns that their condition might deteriorate, and are often unaware that COPD can cause death even though they worry about the manner of their death, especially a fear of dying with breathlessness or suffocation. These issues and fears are not always discussed with a caregiver (Gardiner, 2009). Patients with COPD adapt to an “abnormal normal” life style and accept their limitations rather than express a desire or need for assistance (Habraken, 2008; Panos, 2013). During exacerbations or episodes of breathlessness, they “tough it out” rather than seek medical attention or increased medication use (Panos, 2013). A cross sectional study of interviews with 163 patients with severe COPD showed that 57% had severe breathlessness and 92% said breathlessness was their most important problem (White, 2011). Despite its chronicity, patients and their families often lack information about COPD, its consequences, treatment, effects on psychosocial well-being, and inevitable decline in health. (Table 19.3)

**Table 19.2: COPD’s Effects on Patients’ Lives (Panos, 2013)**

<table>
<thead>
<tr>
<th>Effects of COPD</th>
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<tbody>
<tr>
<td><strong>Physical and Functional Limitations:</strong></td>
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<tr>
<td>– Work and employment constraints</td>
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<tr>
<td>– Recreation restrictions</td>
</tr>
<tr>
<td>– Limits on activities of daily living</td>
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<tr>
<td>– Reduced sexuality</td>
</tr>
<tr>
<td>– Concerns about housing and finances</td>
</tr>
<tr>
<td>– Physical symptoms</td>
</tr>
<tr>
<td><strong>Restricted Social Interactions/Altered Social Networks:</strong></td>
</tr>
<tr>
<td>– Altered relationships with friends and family</td>
</tr>
<tr>
<td>– Reliance upon family and care givers;</td>
</tr>
<tr>
<td><strong>Emotional Effects:</strong></td>
</tr>
<tr>
<td>– Reduced self-worth</td>
</tr>
<tr>
<td>– Vulnerability</td>
</tr>
<tr>
<td>– Depression</td>
</tr>
<tr>
<td>– Hopelessness</td>
</tr>
<tr>
<td>– Fear</td>
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<tr>
<td>– Lack of control</td>
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</table>

(Panos, 2013). The trajectory of decline is not predictable for an individual patient with COPD.
Disease trajectory is difficult to predict in COPD. Although multivariate predictive models have greatly improved prognostication in COPD, there is significant individual variation and uncertainty. This prognostic imprecision may contribute to providers’ timidity and tentativeness in initiating palliative or end of life discussions with patients with COPD. Although patients frequently request predictive information by asking “How long do I have to live?”, primary care providers feel ill prepared to respond, believe that patients want more accurate predictions than they can provide and will then judge them based upon their response, and prefer to reinforce positive prospects (Rogg, 2009; Christakis, 1998).

In general, patients with COPD have a very poor prognosis after an exacerbation. In the 1990’s, patients older than 65 years admitted to an ICU with a COPD exacerbation had a 30% mortality which increased to 60% over the ensuing year (Seneff, 1995). Although this mortality rate has declined to 28%, 48%, and 74% at 1, 2, and 5 years after an initial acute exacerbation treated with noninvasive ventilation in the early 21st century, the prognosis for patients with COPD who experience exacerbations remains poor. (Chung, 2010). Overall mortality in the year after hospitalization for a COPD exacerbation may be as high as 23–50% (Groenewegen, 2003; Chung, 2010; Batzlaff, 2014) but the 6 month mortality rate for elderly patients with mild COPD admitted with nonacidotic COPD exacerbations is 20% (Ranieri, 2008). A retrospective review of patients admitted to the medical intensive care unit from 1995 to 2009 revealed a one year mortality of 50% and that age and hospital length of stay were independent determinants of death (Batzlaff, 2014). Nearly 4 of every 5 patients hospitalized for a COPD exacerbation die within 9 years and the median

<table>
<thead>
<tr>
<th>Burden of COPD on Patients and their Social Support Networks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
</tr>
<tr>
<td>- Intractable and inexorable dyspnea</td>
</tr>
<tr>
<td>- Reduced self-efficacy</td>
</tr>
<tr>
<td>- Poor quality of life</td>
</tr>
<tr>
<td>- Fatigue</td>
</tr>
<tr>
<td>- Disability</td>
</tr>
<tr>
<td>- Social isolation</td>
</tr>
<tr>
<td>- Anxiety depression</td>
</tr>
<tr>
<td>- Family/Caregivers should be aligned under Patients and should not have a – in front of it because it is an equivalent subject heading in the table</td>
</tr>
<tr>
<td>- Insidious encroachment upon their lives</td>
</tr>
<tr>
<td>- Medical, psychosocial care</td>
</tr>
<tr>
<td>- Lack of supportive services</td>
</tr>
</tbody>
</table>

**Table 19.3: COPD Burden for Patients and Family/Caregivers (Yohannes, 2007; White, 2011)**
survival is approximately 1000 days for those with severe airflow obstruction and 2500 days for those with mild disease (Gudmundsson, 2012). However, up to 30% of patients with severe COPD have not been hospitalized in the preceding 2 years (White, 2011).

Comorbidities, especially cardiovascular disease and cancer, are the major causes of death in individuals with less severe airflow limitation whereas respiratory failure is the top cause of mortality in those individuals with worse physiological obstruction. (See Chapter 10, COPD Is a Multi-organ Disorder: Systemic Manifestations) Thus, it is very difficult to predict the disease course in COPD and unexpected deaths occur frequently whereas other patients with severe derangements of lung function may survive for long periods of time (Fox, 1999; Coventry, 2005).

19.5 Advanced Care Planning Discussions Between Providers and Patients with COPD and Their Families

Very few patients with COPD have end of life or palliative care discussions with their providers and fewer still are actually offered these services. Only 13% of National Health Service units in the UK provided end of life care information to patients with stable COPD (Royal College of Physicians, 2008). Only 19% of patients with COPD entering pulmonary rehabilitation had discussed advanced directive plans with their physician (Heffner, 1996). A survey of 115 Veterans with COPD requiring supplemental oxygen demonstrated that only 32% reported a discussion about end of life issues with their self-identified primary COPD provider (Knauft, 2005). Although the majority of general practitioners in the UK believe that discussions of prognosis are important for patients with COPD, most did not have these discussions with their patients and approximately half were undecided as to whether patients wanted to know their prognosis (Elkington, 2001). Only 13% of pulmonologists discussed advanced care planning with most patients, 31% with half, 50% with few, 6% with none or almost none. Although most pulmonologists, 57%, preferred outpatient conversations, most discussions occurred as inpatients. The key elements discussed were diagnosis, treatment purpose, and incurability of COPD; items that were not discussed included appointment of a health care proxy, patients’ values and goals, and palliative care options (Smith, 2013). Comparative studies suggest that the prevalence of end of life discussions between providers and patients with COPD is low and there are significant differences in the quality of COPD prognosis discussions internationally (Mulcahy, 2005; Janssen, 2011). Impediments and promoters of advanced care planning discussions are presented in Table 19.4.

Not only are patients under- or mis-informed about COPD and its management and natural history, but their families frequently have inadequate information about the diagnosis, prognosis, and management (Patel, 2012). Family and friends assist 95% of patients with COPD with household tasks, personal care, or medications
Integrating Supportive, Palliative, and End of Life Care for COPD during the last year of life (Elkington, 2005). Nearly 40% were not aware that their relative with COPD might die even though most would have preferred to have known (Elkington, 2005). Caring for individuals with COPD profoundly affects care providers and the nature of their caring tasks, relationship to the patient, and expectations evolve as the disease progresses (Philip, 2014). There are multiple barriers to identifying patient care givers including a gradual transition into the caring role during which the care giver does not recognize the adoption of this function, the care giver role’s insidious encroachment upon the care giver’s self needs, and ambiguous responsibility and relationship of health care providers to care givers (Carduff, 2014). Despite the

Table 19.4: Factors Aiding and Impeding Palliative Care Discussions (Knauft, 2005; Gott, 2009; Patel, 2012)

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<thead>
<tr>
<th>Patient and Physician Impediments and Promoters for Discussions about Palliative and End of Life Care</th>
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</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
</tr>
<tr>
<td>- Impediments</td>
</tr>
<tr>
<td>- Preference for life maintaining rather than end of life discussion</td>
</tr>
<tr>
<td>- Multitude of providers with uncertainty as to which provider will discuss prognosis and care decisions</td>
</tr>
<tr>
<td>- Negative stigma of a perceived self-induced disease</td>
</tr>
<tr>
<td>- Lack of or incorrect medical information</td>
</tr>
<tr>
<td>- Promoters</td>
</tr>
<tr>
<td>- Family or friends who have died</td>
</tr>
<tr>
<td>- Trust in medical provider</td>
</tr>
<tr>
<td>- Sense of confidence in medical provider’s competence</td>
</tr>
<tr>
<td>- Caring relationship with provider</td>
</tr>
<tr>
<td>- Confidence in provider’s reliability</td>
</tr>
<tr>
<td>- Prior illness</td>
</tr>
<tr>
<td>- Worry about becoming a burden for friends and family if illness progresses</td>
</tr>
<tr>
<td>- Concern about future quality of life</td>
</tr>
<tr>
<td><strong>Physicians</strong></td>
</tr>
<tr>
<td>- Impediments</td>
</tr>
<tr>
<td>- Inadequate time/reimbursement for discussion</td>
</tr>
<tr>
<td>- Imperfect predictive information about the course of COPD</td>
</tr>
<tr>
<td>- Lack of consensus about when, where, and with whom these discussions should occur</td>
</tr>
<tr>
<td>- Connotations of comparing COPD with cancer</td>
</tr>
<tr>
<td>- Potential/perceived conflict between chronic disease management goals and advanced care planning</td>
</tr>
<tr>
<td>- Poor understanding and training in palliative care and end of life care</td>
</tr>
<tr>
<td>- Uncertainty about how patients perceive the discussion of COPD prognosis</td>
</tr>
<tr>
<td>- Promoters</td>
</tr>
<tr>
<td>- Good relationship between provider and patient</td>
</tr>
<tr>
<td>- Experience with lung disease</td>
</tr>
<tr>
<td>- Patient’s prior exacerbations and severity of illness</td>
</tr>
<tr>
<td>- Duration of relationship with patient</td>
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</table>
apparent importance of family and friend care providers for individuals with COPD and their involvement in surrogate end of life decision making, very little is known about their needs, requirements, and involvement in the advanced care planning process (Caress, 2009).

19.6 Timing and Content of Discussions

19.6.1 Early Stage COPD

The entire spectrum of advanced care planning can be overwhelming to patients, their families, and health care providers. Therefore, the goals of these discussions may evolve with the course of disease; however, very little is known about the structure, content, or frequency of advanced care planning during the early stages of COPD as most research has studied the latter stages of COPD. The time of diagnosis is an opportunity to begin to educate both the patient and their family about COPD, its management, and its natural history. As a part of chronic disease management, advanced care planning should begin at the time of diagnosis. (Figure 19.1) There are few if any guidelines for approaching advanced care planning at this stage of COPD but providers should present a realistic picture of the disease and its course. Back and colleagues (Back, 2003) have advocated a “hope for the best, and prepare for the worst” agenda for patients with advanced disease but it is not known if this approach is ideal or how it is received by patients and their families during the early stages of COPD. Recent advances in management and improvements in outcomes (discussed in Chapters 14, Management of Stable COPD; 16, Management of Outpatient COPD Exacerbations; 17, Management of Inpatient COPD Exacerbations) should be discussed. Dialogue about advanced directives, appointment of surrogate healthcare decision makers, and promotion of familial discussions about health and contingencies for care might be initiated during this period. In subsequent discussions, the provider can begin discussions of palliative care and end of life issues including review of advanced directives and surrogate healthcare decision makers, use of mechanical ventilation, critical care, and resuscitation status. Involvement of care providers is essential as COPD progresses and patients became more reliant upon others (see Chapter 13, Psychosocial and Familial Consequences of COPD). The extent and breadth of these discussions can be daunting to providers, patients, and their families and they are best approached incrementally once open avenues of dialogue are established between the provider and patient and family. Although referral to multidisciplinary services may also facilitate these discussions, most palliative and hospice care teams become involved with patients during later stage disease (Cambell, 2014; Curtis, 2014; Dando, 2014).
19.6.2 Later Stage COPD

The timing of advanced care planning discussions for the latter stages of COPD is difficult because the disease trajectory and natural history varies widely. Many studies have attempted to identify the characteristics of individuals with COPD who have a limited, less than one year, prognosis. (Table 19.5)

Table 19.5: Indications for End of Life Discussions with Patients who have COPD (Curtis, 2008; Benzo, 2013; Reinke, 2008; Matkovic, 2012)

<table>
<thead>
<tr>
<th>Characteristics of Candidates for End of Life Discussion</th>
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<tbody>
<tr>
<td>– FEV1 &lt; 30% predicted</td>
</tr>
<tr>
<td>– Supplemental oxygen therapy</td>
</tr>
<tr>
<td>– One or more COPD exacerbations in the prior year requiring hospital admission, especially if associated with either hypoxemia or hypercarbia</td>
</tr>
<tr>
<td>– Left heart failure/other comorbidity</td>
</tr>
<tr>
<td>– Weight loss/cachexia</td>
</tr>
<tr>
<td>– Reduced functional status causing activity limitations/change to a very sedentary life style</td>
</tr>
<tr>
<td>– Increasing dependence upon others</td>
</tr>
<tr>
<td>– Age &gt; 70 years</td>
</tr>
<tr>
<td>– Decrease in gait speed or distance walked in 6MT</td>
</tr>
<tr>
<td>– Decrease in maximal inspiratory pressure</td>
</tr>
<tr>
<td>– Feeling downhearted or upset</td>
</tr>
<tr>
<td>– Decline in PaO$_2$ by 5 mm Hg</td>
</tr>
<tr>
<td>– Increase in PaCO$_2$ by 3 mm Hg</td>
</tr>
</tbody>
</table>

These characteristics can help health care providers recognize individuals with COPD who are candidates for palliative and end of life advanced care planning. For those individuals who have not yet started the advanced care planning process, this recognition is critical for the initiation and possible acceleration of advanced care planning if discussions about palliative care, hospice, advanced directives, and end of life management have not yet been initiated. For those in whom the planning process has started, the development of these signs and symptoms is a signal to progress to the next stage of planning (Seamark, 2007).

In 2000, a comparison study of 100 patients, half with COPD and half with non-small cell lung cancer, showed that, whereas 30% of patients with lung cancer received palliative care services, none of the patients with COPD received palliative care (Gore, 2000). More recently, in 2013, only 20% of patients with COPD were referred to palliative care compared with 34% of patients with heart failure, 37% with severe dementia, and 60% with cancer (Beernaert, 2013) despite worse quality of life among those with COPD compared with advanced nonsmall cell lung cancer (Habraken, 2009). Further, among patients who do not receive palliative care consultations, those with COPD more often received curative or life-prolonging treatments and less often palliative
or comfort management compared with patients with other chronic disorders (Beer-naert, 2013). The Study to Understand Prognosis and Preferences for Outcomes and Treatments (SUPPORT, 1999) enrolled patients with nine chronic disorders including COPD in five American hospitals (SUPPORT, 1999; Claessens, 2000). Although most patients with COPD preferred comfort rather than life prolonging treatment, they were more likely to experience severe breathlessness, be placed on mechanical ventilator support in an intensive care unit, and receive tube feedings and cardiopulmonary resuscitation than patients with lung cancer (Claessens, 2000). During the last 6 months of life, Veterans with COPD received fewer opiates and benzodiazepine prescriptions, were twice as likely to be admitted to an ICU, had longer ICU length of stays, and greater healthcare costs than Veterans with lung cancer (Au, 2006). The median time between palliative care referral and death was only 10 days for patients with COPD compared with 20 days for those with cancer in the Flanders Study to Improve End-of-Life Care and Evaluation Tools (FLIECE-project) (Beernaert, 2013).

Although patients with COPD desire information about diagnosis, management, prognosis, death, and advanced care, they prefer these discussions occur when they are in relatively good health (Hardin, 2008; Gardiner, 2009; Reinke, 2008). Even though most patients with COPD desire better education and information about their condition and feel they have not received enough information about their prognosis and future care, they often prefer deferring end of life discussions until their disease is more advanced (Gore, 2000; Gysels, 2010; Gaber, 2004). Very often, patients expect their providers to initiate advanced care discussions and, when these topics are not discussed, assume that advanced care is not relevant to them (McCormick, 2009). However, even when advanced care discussion is offered, some patients will not engage due to denial or fear of COPD (Gardiner, 2009). Most patients do not want to receive detailed information that they perceive as distressing and prefer broad indications of prognosis (Gore, 2000). Some patients with COPD may prefer to focus discussions on alleviation of symptoms rather than end of life care (White, 2011). Others prefer not to discuss end of life and these individuals usually describe an excellent prognosis, good quality of life, and do not want to be involved actively in decision making (Barclay, 2009; Hoffman, 1997). COPD comorbidities, especially anxiety and depression, may also impede patients and their families from engaging in advanced care discussions and may influence their decisions about mechanical ventilation and resuscitation (Simpson, 2008; Omachi, 2010; Stapleton, 2005). There is limited awareness and understanding of palliative care among individuals with COPD (Fahim, 2013). Providers report that end of life discussions occur late in the course of COPD, often when patients are unable to make decisions (Gott, 2009; Sullivan, 1996). They are uncertain when to discuss end of life with patients with COPD and rarely have these discussions early in the disease course (Gott, 2009; Momen, 2012).

The quality of patient-provider discussions of end of life care for COPD can be improved. One trial showed that when providers received a one page report summarizing a patient’s responses to a questionnaire eliciting their preferences for commu-
nication, life-sustaining therapy, and experiences at the end of life, the number of discussions increased to 30% from 11% compared with providers who did not receive a report (Au, 2012). In addition, patients in the intervention group felt that the quality of the discussions was better. Experiential skills building communication training also enhances providers’ proficiency with end of life communication (Fallowfield, 2002; Back 2007).

19.7 Symptom Management

19.7.1 Dyspnea

Breathlessness is the principal respiratory symptom affecting patients with COPD. Breathlessness in COPD may be multifactorial with contributions from bronchospasm, dynamic hyperinflation, comorbidities especially heart failure and anemia, muscle weakness, anxiety and fear. Bronchospasm is often amenable to treatment with beta agonist and anticholinergic bronchodilators (discussed in management of stable COPD and COPD exacerbations). Dynamic hyperinflation is caused by airtrapping and may be reduced by bronchodilators, reduction in respiratory rate, and breathing techniques such as pursed lip breathing (discussed in management of stable COPD). Heart failure is treated with diuretics, nitrates, and afterload reduction. Red blood cell transfusions may alleviate breathlessness associated with anemia. Muscle weakness may cause decreased minute ventilation and hypercarbia that may be improved with noninvasive ventilation. Anxiolytics such as benzodiazepines may alleviate anxiety and fear. A 2010 Cochrane analysis found that benzodiazepines provided no significant benefit for the relief of breathlessness in patients with COPD (Simon, 2010). Benzodiazepines caused less drowsiness than morphine but more than placebo.

Qualitative studies show that opioids provide a sense of calm, improved quality of life, and relieved dyspnea in patients with COPD. Caregivers noted that opioids helped patients to breath more normally, improved their anxiety and depression while also reducing caregivers’ anxiety. However, physicians were reluctant to prescribe opioids for severe breathlessness due to lack of knowledge and experience and concerns about untoward effects and legal consequences (Rocker, 2012). Although opiates are effective treatment for breathlessness in individuals with COPD, concern has been raised that opiates may cause respiratory depression and thus accelerate death (Varkey, 2010). The principle of double effect proposes that, when appropriately used with the intent of relieving suffering, opiates may be administered to relieve breathlessness or pain even if they might hasten death (Sulmasy, 1999; Quill, 1997). Observational studies suggest that, when appropriately used, opiates do not hasten death (Chan, 2004; Bercovitch, 1999; Sykes, 2003). Enteral or intravenous routes are preferred as review of nebulized morphine trials suggest that this route of administration is not effective for the relief of refractory dyspnea (Brown, 2005; Foral, 2004).
The perception of breathlessness is mediated through peripheral and central nervous system pathways and influenced by physical, psychosocial, and spiritual factors (Davidson, 2011). Supplemental oxygen prolongs life for individuals with COPD who are hypoxemic at rest despite maximal pharmaceutical treatment. Oxygen does not appear to be beneficial in individuals with refractory breathlessness and mild hypoxemia or normoxemia (Davidson, 2011; Abernethy, 2005) even though nearly one third of supplemental oxygen costs in Canada are for palliative care (Abernethy, 2005; Guyatt, 2000). A Cochrane analysis of the treatment of dyspnea with supplemental oxygen in individuals with COPD and mild hypoxemia or normoxemia demonstrated that oxygen can effectively reduce breathlessness but that oxygen treatment should be evaluated on an individual basis and discontinued if it is ineffective (Uronis, 2011). However, a subsequent double blind randomized trial comparing room air with oxygen in patients with refractory dyspnea demonstrated no benefit (Abernethy, 2010). Compared with compressed air, oxygen does not improve dyspnea, quality of life, or functional status in home based, nonhypoxemic patients with COPD (Moore, 2011). Mixtures of oxygen and helium may help relieve breathlessness in individuals with COPD but have not been evaluated in large, long term trials (Laude, 2007).

Nonpharmacological treatments, including breathing training, walking aids, neuro-electrical muscle stimulation, and chest wall vibration, were found to be effective treatments for breathlessness in a Cochrane review in 2008 (Bausewein, 2008); that review is currently undergoing revision (Bausewein, 2013).

19.7.2 Anxiety and Depression

Pharmacologic management of anxiety and depression in individuals with COPD has only recently been evaluated and their treatment in palliative care of patients with COPD is even less well studied (see Chapter 13, Psychosocial and Familial Consequences of COPD).

Comprehensive, multidisciplinary pulmonary rehabilitation ameliorates anxiety and depression in patients with moderate to severe COPD as well as improves quality of life and exercise capacity (Coventry, 2009; Coventry, 2011; McCormick, 2009).

19.7.3 Other Symptoms

Patients with COPD may have significant comorbidities, anorexia, cachexia, poor nutritional intake, and fatigue. Management of these symptoms is discussed in chapters on comorbidities and management of stable COPD. Lung volume reduction surgery reduces the rate of decline in quality of life of individuals with COPD, especially those with upper lobe predominant emphysema (Benzo, 2009).
19.8 Bereavement

Advanced care planning does not end with death; care for both the patient’s family/friends as well as health care providers should be part of the advanced care plan. (Figure 19.1) Caretakers of individuals with COPD experienced carer burden, limited access to support services, and need for both palliative and bereavement support (Hasson, 2009).

19.9 Effectiveness of Palliative Care

Advanced care planning improves patient satisfaction, increases the proportion of at home deaths, and use of hospice services (Tierney, 2001; Hammes, 1998). Provider goals of advanced care planning are outlined in Table 19.6.

Table 19.6: Goals for Advanced Care Planning (Halliwell, 2004)

<table>
<thead>
<tr>
<th>Provider Goals for Advanced Care Planning</th>
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</thead>
<tbody>
<tr>
<td>- Awareness of the implications of a COPD diagnosis</td>
</tr>
<tr>
<td>- Use of uncertainty to ease discussion</td>
</tr>
<tr>
<td>- Building relationships with patients</td>
</tr>
<tr>
<td>- Being caring and respectful</td>
</tr>
<tr>
<td>- Beginning discussion early in the disease course</td>
</tr>
<tr>
<td>- Identifying and using opportunities to discuss prognosis</td>
</tr>
<tr>
<td>- Working as a team</td>
</tr>
</tbody>
</table>

The COPD IMPACT study evaluated a customized home-based palliative care service for patients and caregivers and found, that although palliative care services were valued, health related quality of life, caregiver burden and symptom severity did not change (Horton, 2013). Despite a desire to die at home with supportive care, many patients died in hospital because patients’ needs exceeded caregivers’ ability to cope precipitating hospital admission (Horton, 2013). A Cochrane review of home palliative services for individuals with multiple disorders including COPD concluded that home palliative care improved the chances of dying at home and reduced symptom burden but did not affect caregiver grief (Gomes, 2013). Thus, there are conflicting reports on the benefits of palliative and hospice care for individuals with COPD. Differences in program components, level of involvement, and COPD stage at the initiation of services may be variables that influence a program’s effectiveness.
19.10 Conclusion

COPD is a chronic, progressive disorder that is treatable but not curable. The natural course of COPD is marked by exacerbations, episodes of increased respiratory symptoms, and development of nonpulmonary co-morbidities. Many current treatments reduce the frequency and severity of COPD exacerbations and may improve survival. Advanced care planning is the process through which providers communicate with patients and their families/support networks to prepare a comprehensive COPD management strategy and integrate therapeutic, supportive, palliative, and end of life care. Because the disease trajectory is unpredictable for an individual patient with COPD, advanced care planning should begin at the time of diagnosis by providing both the patient, their family, and support network education about COPD, its management, and its natural history. As a part of chronic disease management, dialogue about advanced directives, appointment of surrogate healthcare decision makers, and promotion of familial discussions about health and contingencies for care should be initiated. In subsequent discussions, the provider can begin discussions of palliative care and end of life issues including review of advanced directives and surrogate healthcare decision makers, use of mechanical ventilation, critical care, and resuscitation status. Involvement of care providers is essential as COPD progresses and patients became more reliant upon others. Breathlessness is the most severe and devastating symptom of COPD; effective treatments depend upon the cause but include bronchodilators, oxygen, pulmonary rehabilitation, and opiates.

19.11 Summary Points

1. Although there are many effective treatments for COPD, there is no cure and many patients die of or with COPD.
2. Advanced care planning is the process through which providers communicate with patients and their families and support networks to prepare a comprehensive COPD management program that incorporates therapeutic, supportive, palliative, end of life, and bereavement care.
3. Because the disease trajectory for an individual patient is highly variable and unpredictable, advanced care planning for COPD should begin at the time of diagnosis and incrementally proceed as the disease progresses.
4. Effective treatments for the management of breathlessness, anxiety, and depression associated with COPD include pharmacologic and nonpharmacologic interventions.
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Goode, Erich.
GOLD
glucocorticoids
genetics
gender differences
fracture
Frequent exacerbator
fumes
functional status
gender differences
health genetics
Global Initiative for Chronic Obstructive Lung Disease
Goede, Erich. see moral panic
granzyme B
Handihaler®
healthcare
healthcare costs
healthcare utilization
health related quality of life
Heart failure
Heart Failure
histone deacetylase
history
HIV
hospice
Hospital at home
hospitalization
hospitalizations
human immunodeficiency virus
Hydralazine
hydrofluoroalkanes
hypercapnia
hypercarbia
hyperinflation
hypertension
hypopneas
hypopneas
hypoventilation
hypoxemia
ICA
ICU
IFNy
IL-4
IL-5
IL-8
immune function
inflammation
inhaled corticosteroids
inhaler
Inhaler Education
insomnia
inspiratory muscle training
Integrated Care Teams
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interstitial lung disease
Interventions
Interventions
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