Chapter 15

Chronic Lower Respiratory Tract Diseases

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INTRODUCTION

Chronic respiratory diseases are common and increasing in relative terms as causes of disability and death. They refer to noninfectious conditions of the lung and respiratory tract, excluding cancers and trauma. In the *International Classification of Diseases*, they are covered mostly in chapter X (table 15.1) (WHO 2010). This chapter focuses on the more common of these conditions, but we have been influenced by the availability of data. Not addressed are two common conditions of the upper respiratory tract—allergic and chronic rhinosinusitis—that cause considerable disability but are not associated with substantial mortality. Smoking cessation and reduction or elimination of other harmful exposures is an important component of the management of any chronic respiratory disease. Tobacco cessation is addressed in chapter 4 in this volume (Roy and others 2017) and in chapter 10 of volume 3 (Jha and others 2015).

The two main conditions contributing to death and disability are asthma and chronic obstructive pulmonary disease (COPD). Both are clinical diagnoses and are associated with narrowed airways and difficulty exhaling. Asthma has become more common in many countries in parallel with increasing prevalence of allergic sensitization. COPD, in particular, is an increasing burden as the world's population ages and tobacco smoking increases in many low- and middle-income countries (LMICs), especially among women. The effects of both diseases and mortality from all causes tend to be greater in persons with smaller lungs, and smaller lung volumes are more common in LMICs.

Although these diseases are rarely curable, effective treatments to reduce both disability and death are available and affordable.

DISTRIBUTION OF DISEASE, DISEASE BURDEN, RISK FACTORS, AND PRIMARY PREVENTION

Asthma

Asthma is a common cause of morbidity in children and adults; it is generally amenable to treatment with effective low-cost medications that have minimal long-term adverse side effects. An estimated 300 million people worldwide suffer from asthma; more than 250,000 asthma-related deaths occur annually. Asthma ranks forty-second in the list of diseases and conditions that cause death globally (Lozano and others 2013), but fourteenth in the list of causes of years lived with disability (Salomon and others 2012; Vos and others 2012). The disease generally has an early onset and tends to persist throughout life; deaths among young people with asthma are rare.

The prevalence of asthma has been increasing, although this increase may be slowing or even reversing in some countries. In LMICs, very low prevalence has been recorded in rural compared with urban environments (Calvert and Burney 2005; Keeley and Gallivan 1991;

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Table 15.1 Principal Rubrics of the International Classification of Diseases, 10th Revision, Covered in This Chapter

J40–J47 Chronic lower respiratory diseases:
• J40 Bronchitis, not specified as acute or chronic
• J41 Simple and mucopurulent chronic bronchitis
• J42 Unspecified chronic bronchitis
• J43 Emphysema
• J44 Other chronic obstructive pulmonary disease
• J45 Asthma
• J46 Status asthmaticus
• J47 Bronchiectasis
J60–J70 Lung diseases due to external agents:
• J60 Coalworker's pneumoconiosis
• J61 Pneumoconiosis due to asbestos and other mineral fibres
• J62 Pneumoconiosis due to dust containing silica
• J63 Pneumoconiosis due to other inorganic dusts
• J64 Unspecified pneumoconiosis
• J65 Pneumoconiosis associated with tuberculosis
• J66 Airway disease due to specific organic dust
• J67 Hypersensitivity pneumonitis due to organic dust
• J68 Respiratory conditions due to inhalation of chemicals, gases, fumes and vapours
• J69 Pneumonitis due to solids and liquids
• J70 Respiratory conditions due to other external agents
J80–J84 Other respiratory diseases principally affecting the interstitium:
• J84 Other interstitial pulmonary diseases

Source: WHO 2010.

Perzanowski and others 2002), but the prevalence in LMICs is likely to rise as they become more urbanized. The increased prevalence in urban populations is associated with an increase in positive skin tests to allergens, which is explained in part by increases in body mass index (Calvert and Burney 2005) and in part by the quality of the urban diet (Hooper and others 2008). Within urban communities, socioeconomic deprivation is associated with more frequent symptoms and exacerbations of asthma, use of emergency services, hospitalizations, and mortality, likely due to lower access to effective therapy and health services (Poyser and others 2002).

Consistent with these findings, prevalence rates vary widely for children and adults. The first phase of the International Study of Asthma and Allergies in Childhood provided findings for 463,801 children ages 13–14 years (155 centers in 56 countries) and 257,800 children ages 6–7 years (91 centers in 38 countries) (Asher and others 1998). The prevalence of asthma symptoms was based on a positive response to the question, "Have you had wheezing or whistling in the chest in the last 12 months?" For younger and older children, there was an approximate 20-fold range of prevalence, with the highest rates generally in countries with high gross national income (GNI) as defined by the World Bank, but severe asthma was proportionally more common in low-income areas of Africa and South and South-East Asia (Lai and others 2009).

The World Health Survey interviewed adults older than age 18 years on six continents using questions derived from the European Community Respiratory Health Survey on wheezing and on diagnosed asthma (Sembajwe and others 2010). The prevalence of diagnosed asthma ranged from 2 percent in Vietnam to 33 percent in Australia. The lowest mean prevalence was found in middle-income countries; however, the percentage of sites with prevalence greater than 10 percent rose from 19 percent (4 of 21) in the countries with the lowest income (less than US$3,000) to 59 percent (10 of 17) in countries with intermediate incomes (US$7,999) and to 73 percent (22 of 30) in countries with per capita incomes greater than US$8,000 per year.

Asthma runs in families, but the basis for inheritance is complex; the observation that up to 30 percent of childhood asthma is related to genetics needs further study (Moffatt and others 2010), but evidence for heritability is less strong for adults. Asthma is associated with allergy, and both allergy and allergic asthma are less common in poorer countries (Weinmayr and others 2010); nonallergic wheeze is distributed fairly evenly by levels of poverty. Many risk factors have been associated with the onset of disease and with disease exacerbations. Risk factors for disease onset that are potentially remediable include parental (and even grandparental) smoking, obesity, poor diet, and workplace exposure to allergens. Evidence for dietary factors preventing asthma is inconclusive; studies with improved design are needed (Nurmatov, Devereux, and Sheikh 2011). Adult-onset asthma caused by occupational exposures are preventable by appropriate measures to limit exposures in the workplace and by screening of exposed workers to detect early signs of disease. Exacerbations are associated with viral upper respiratory tract infections, especially in children, and with exposure to airborne allergens in the outdoor environment; these factors are more difficult to avoid.

Most people with asthma develop symptoms in childhood. During adolescence, symptoms of the disease remit in up to 40 percent of cases; however, in approximately 50 percent of these cases, for unknown reasons, symptoms return during adult life. Asthma that begins in adult life tends to be more severe and is more

common in women; exposure to cigarette smoke and an inadequate intake of antioxidants may play a role (Larkin and others 2015).

Death rates from asthma are relatively low, but are higher in older adults than in children or young adults (Lozano and others 2013). In countries with efficient programs for diagnosing and treating asthma, death rates of less than 1 per 1 million population are being achieved. Accordingly, from a public health perspective, asthma deaths need to be viewed as preventable. Poorly controlled asthma is also a risk factor for the development of fixed airway obstruction in later life (Obaseki and others 2014).

Chronic Airway Obstruction and COPD

Chronic airway obstruction is defined as the ratio of one-second forced expiratory volume (FEV_1) to vital capacity (VC). FEV_1 is the volume of air that can be blown out with maximum force from a full inspiration in one second. VC is the maximum volume of air that can be expired from a full inspiration in one breath and is generally measured as forced vital capacity (FVC) in the same maneuver as FEV_1. VC and FVC are measures of lung size, and FEV_1 is a measure of flow over the first second of expiration; the FEV_1/FVC ratio is a measure of flow adjusted for lung size.

This section focuses on irreversible obstruction: the presence of a low FEV_1/FVC ratio following administration of a bronchodilator. There has been debate about the best index for measuring irreversible obstruction. The Global Initiative for Chronic Obstructive Lung Disease (GOLD 2014) has recommended a single index for all ages—a fixed FEV_1/FVC ratio of 0.7. However, because this ratio declines universally with age, an alternative approach is to define a low ratio as being a value below the lower limit of normal (Miller and others 2005; Swanney and others 2008). The lower limit of normal is the level of FEV_1/FVC exceeded in 95 percent of the normal population, generally defined as persons who have never smoked and have no respiratory diagnosis and (sometimes) no respiratory symptoms. This measure takes account of the person's age. The ratio is affected by age and disease, but does not seem to be affected by other factors, such as height, gender, and ethnicity (Hankinson, Odencrantz, and Fedan 1999).

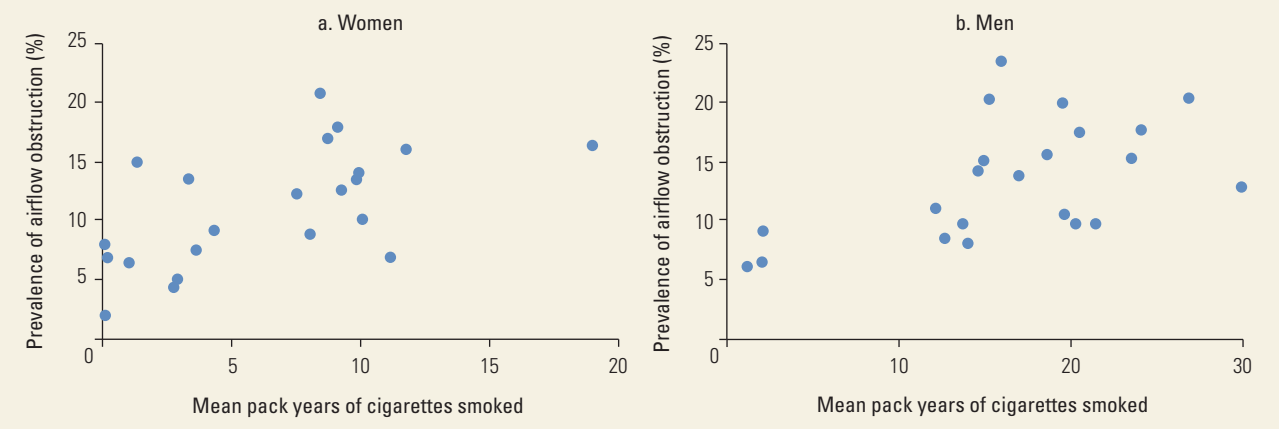
COPD is the most common cause of chronic airflow limitation. In COPD, obstruction arises because the small airways either are narrowed or are obstructed by inflammation (small airway disease) or because, as in emphysema, lung tissue is destroyed and loses elasticity, which is required for keeping airways open during exhalation. In chronic asthma, bronchoconstriction, that is, thickening of airway walls due to predominantly allergic inflammation, edema, an increase in smooth muscle, and some subtle scar tissue, narrows the airways.

Lung function may be tested before or after inhalation of a bronchodilator to increase the caliber of the airway. Prebronchodilator obstruction that reverses after a bronchodilator is administered is described as reversible obstruction, and demonstrating this at some stage is considered necessary for the diagnosis of asthma. Up to two-thirds of patients with COPD show evidence of improvement of obstruction, but it is generally of a lesser magnitude. Increases of more than 400 milliliters (ml) suggest a diagnosis of asthma. Among the normal population, 95 percent have an increase of FEV_1 of less than 12 percent of baseline value following administration of 200 micrograms inhaled salbutamol (Tan and others 2012).

Although family studies suggest that approximately 50 percent of the variation in lung function is due to genetic factors, only a very small part of this variation has been attributed to specific genes (Loth and others 2014). Globally, the most common reason for a low postbronchodilator FEV_1/FVC ratio is smoking. Smoking in adolescence prevents FEV_1 from developing to its full potential (Jaakkola and others 1991); continuing smokers have a dose-related decline in FEV_1 of about 10–15 ml per year greater than that of never smokers, former smokers, or quitters (U.S. Surgeon General 1984). Lung function returns to normal rates on cessation of smoking, but FEV_1 does not recover more than about 200 ml (Dockery and others 1988). Passive smoking is also associated with loss of FEV_1/FVC ratio (Hooper and others 2012). Figure 15.1 shows the prevalence of a low FEV_1/FVC ratio in the Burden of Obstructive Lung Disease study, defined as the lower limit of normal for men and women plotted against the mean pack years of cigarettes smoked (Burney and others 2014). The two measures are strongly associated, as are the ratio and the prevalence of ratios below the lower limit of normal. Where smoking is rare, the prevalence of a low FEV_1/FVC ratio is close to 5 percent, the value expected, by definition, in a normal population without known respiratory disease.

Other associations with chronic airway obstruction include a history of tuberculosis (Allwood, Myer, and Bateman 2013), occupational exposures to dust, a low body mass index, and age (Hooper and others 2012). A history of tuberculosis is more strongly associated with airway obstruction than it is with restrictive spirometry (low FVC) (Hooper and others 2012; Hwang and others 2014; Lam and others 2010; Menezes and others 2007). Studies have found a protective effect

Figure 15.1 Prevalence of a Low FEV_1/FVC Ratio (below the Lower Limit of Normal) in the BOLD Study Plotted against the Mean Pack Years of Cigarettes Smoked



Source: Burney and others 2014.
Note: BOLD = Burden of Obstructive Lung Disease; FEV_1 = one-second forced expiratory volume; FVC = forced vital capacity.

on lung function from a healthy diet, characterized by high intake of fiber, fruits, and vegetables and low intake of simple sugars and saturated fats (Root and others 2014; Shaheen and others 2001). An adverse effect of processed meats has also been described (Varraso and others 2007). There is an association with age after adjustment of lung function for age and for years smoking (Hooper and others 2012). Because the evidence of an association with age comes largely from cross-sectional studies, there are two possible explanations: another environmental risk that is associated with cumulative reduction in FEV_1 and an effect associated with year of birth rather than with age, that is, a birth-cohort effect. The latter effect implies the appearance of a risk factor in early life that has a persistent effect over the life course and that may affect succeeding generations differently.

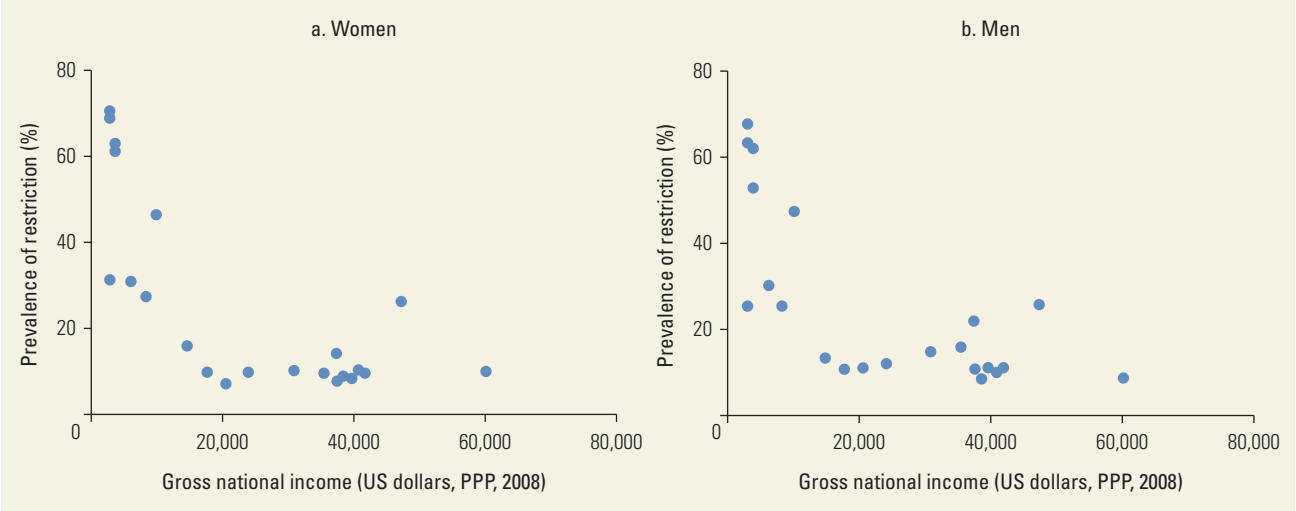
Two risk factors commonly associated with obstruction are air pollution, particularly indoor air pollution, and occupational exposures, but evidence that these risk factors are important is less convincing. They are associated with increased symptoms of bronchitis, frequency of acute exacerbations (lung attacks), and even effects on mortality when lifetime exposures are considered (Hansell and others 2016), but evidence of an effect on the FEV_1/FVC ratio has been less consistent, at least in studies of the general population (Hooper and others 2012; Schikowski and others 2014; Smith and others 2014). It has, however, been argued that a coherence in the evidence relating to different sources of particulate pollution from cigarette smoking, indoor sources, and outdoor sources suggests that all of these factors play a part (Burnett and others 2014).

Idiopathic Low FVC

Low FEV_1 is associated with several comorbidities and an increase in overall mortality. This condition is associated with low total lung capacity (Pedone and others 2012) and low FVC (Burney and Hooper 2011; Fried and others 1998; Kannel and others 1980); it is not associated with airflow obstruction. In clinical medicine, low FVC is generally linked to specific restrictive lung diseases associated with fibrosis, which are relatively rare. A low FVC, however, is common, particularly in poor populations, and rates are strongly associated with annual GNI per capita of less than US$15,000. Figure 15.2 shows the prevalence of low FVC (below the lower limit of normal in the U.S. National Health and Nutrition Examination Survey white population [Hankinson, Odencrantz, and Fedan 1999]) plotted against GNI per capita (Burney and others 2014).

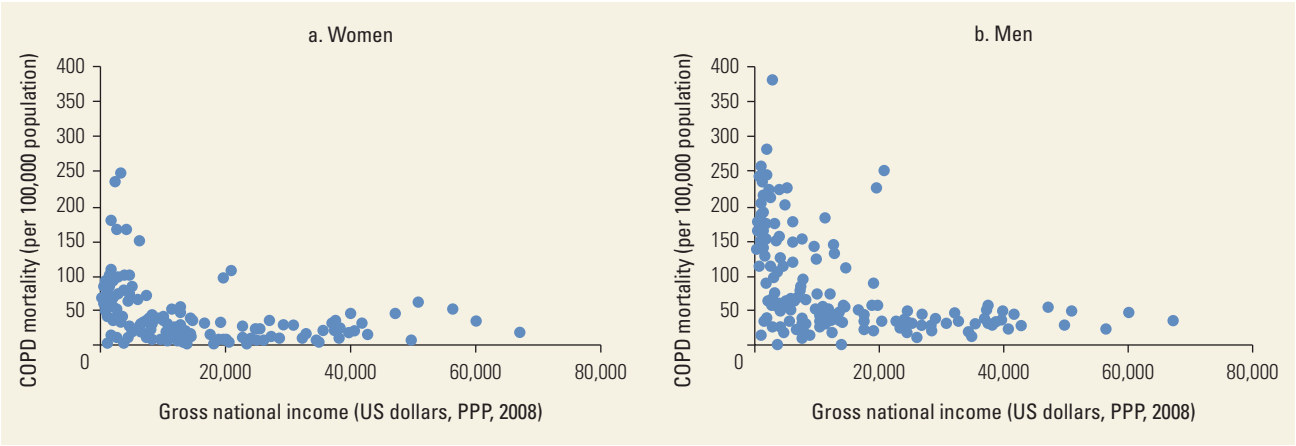
A similar pattern is seen for the distribution of mortality from COPD (figure 15.3), suggesting that the distribution of low FVC is strongly associated with death attributed to COPD. It seems that high mortality rates attributed to COPD are associated more strongly with low lung volumes (FVC) than with obstruction (a low FEV_1/FVC ratio). This observation fits with the evidence on survival among people with a low FEV_1/FVC ratio, which is more or less normal, when adjusted for the other effects of cigarette smoking, whereas people with low FVC have poor survival rates (Burney and Hooper 2011).

Figure 15.2 Prevalence of a Spirometric Restriction (FVC < LLN) Plotted against Annual per Capita Gross National Income



Source: Burney and others 2014.
Note: All participants were ages 40 years or older. FVC = forced vital capacity; LLN = lower limit of normal; PPP = purchasing power parity.

Figure 15.3 Age-Standardized National Chronic Obstructive Pulmonary Disease Mortality (Ages 15 Years and Older), by Gender and Annual per Capita Gross National Income



Source: Burney and others 2014.
Note: COPD = chronic obstructive pulmonary disease; PPP = purchasing power parity.

Historically, the association between low lung volumes and mortality also fits with the association between social class and death from COPD in high-income countries (HICs), where the gradient across social classes has been even greater than that for tuberculosis and far greater than that for lung cancer (U.K. Office of Population Censuses and Surveys 1986), another condition strongly associated with cigarette smoking.

The risk factors for low FVC, apart from poverty, are not well established. A consistent association has been made with low birth weight, confirming that this is at least in part a developmental condition determined early in life (Barker and others 1991; Lawlor, Ebrahim, and Davey 2005). Nutrition might also play a role. In one study, children randomized to receive vitamin A in early life had higher FVCs than those randomized to receive a placebo (Checkley and others 2010), a finding that may be relevant in populations with low intake of vitamin A. A second randomized trial used a much lower dose of vitamin A as part of a multinutrient supplement during pregnancy. No effect on lung function was seen at age eight years (Devakumar and others 2015). Some evidence indicates lower FVC in those exposed to higher levels of air pollution early in life (Schultz and others 2016),

but the evidence has been inconsistent (Fuertes and others 2015). Although the evidence is so far inconclusive, ongoing trials reducing exposure to high levels of particulate pollution in children in low-income settings will be important. Other risk factors for low FVC are even more speculative, but any factors associated with low birth weight could, in theory, also be important.

The influence of ethnicity or race on FVC has been a topic of debate. African Americans have lower FVCs than white Americans of the same age, gender, and height (Hankinson, Odencrantz, and Fedan 1999). This is also true for African, Caribbean, and other ethnic minorities in the United Kingdom (Hooper and Burney 2013) and for Aboriginal Australians (Cooksley and others 2015). However, the common assumption that low FVC is explained by race alone is unwarranted at this time (Lundy Braun, Wolfgang, and Dickersin 2013) for two reasons. First, ethnic minorities in all countries have poorer backgrounds, and because social deprivation has been strongly associated with low FVC, this is a potential confounder (Menezes and others 2015; Sonnappa and others 2015). Second, the mortality for persons with a given FVC, age, height, and gender is the same irrespective of ethnicity, at least in the United States (Burney and Hooper 2012). This finding suggests that, whether the origins are genetic or environmental, the effects are similarly detrimental (Burney and Hooper 2012).

Restrictive Lung Disease and Fibrosis

Reduced maximal lung inflation (restriction) can be caused by chest wall stiffness, respiratory muscle weakness, or one of the many causes of widespread disease of the lung parenchyma that may result in diffuse lung scarring, called *fibrosis*. These diseases, termed idiopathic interstitial pneumonias, have recently been classified by an American Thoracic Society/European Respiratory Society Working Group (Travis and others 2013) and are also collectively referred to as *diffuse parenchymal lung disease* (Antoniou and others 2015). They are relatively uncommon and are further classified into those of known and unknown causes. Known causes include exposure to known fibrosing agents like inorganic or organic dusts. Unknown causes include sarcoidosis and idiopathic pulmonary fibrosis (IPF) (Antoniou and others 2015); IPF is the most common. Best estimates of mortality from IPF are 5–10 cases per 100,000 population (age standardized), and its prevalence appears to be increasing (Hutchinson and others 2014). Adding occupational causes or causes secondary to systemic disease may double or triple the prevalence of diffuse parenchymal fibrotic lung disease (Behr 2009). IPF has a relentless course until death ensues in three to five years, often from acute exacerbation (Travis and others 2013).

The clinical presentation of fibrosing lung diseases is shortness of breath and widespread inspiratory crackles in the lung bases that become more widespread as disease progresses. The chest roentgenogram usually shows diffuse nodular, or linear, opacities of varying size and combinations, depending on the cause; lung function testing shows reduced lung volumes and, in more advanced cases, impairment of gas exchange (respiratory failure). Finger clubbing is a common sign in established disease. Patients presenting with these features require referral because the diagnosis may require specialized procedures and even lung biopsies. High-resolution computed tomography scans of the chest provide useful information and may be sufficient to confirm the diagnosis of IPF in cases in which other clinical features (including history) suggest this diagnosis. Lung biopsies are obtained through a limited thoracotomy or by use of minimally invasive thoracoscopic methods (Aziz and others 2004; Travis and others 2013). In some cases, biopsies can be avoided; the diagnosis can be confirmed by bronchoscopic means that can be combined with use of bronchoalveolar lavage (washings from bronchi), which may provide confirmatory evidence of lung malignancy, hemorrhage into lung tissue, an eosinophilic lung condition, or a chronic infection such as tuberculosis. Transbronchial or endobronchial biopsies are useful when sarcoidosis, an organizing pneumonia, or hypersensitivity pneumonitis is suspected to be IPF. Because the treatments for these different conditions vary widely, definitive diagnosis, sometimes by exclusion, is essential.

Hypersensitivity pneumonitis usually has a benign course, especially with antigen avoidance. Corticosteroids are recommended for severely symptomatic patients with important functional and radiologic abnormalities. In some patients, however, especially those with bird fancier's or pigeon-breeder's lung, the prognosis is worse; some individuals develop severe and progressive fibrosis and cor pulmonale (Glazer 2015).

Lung fibrosis secondary to rheumatic diseases, for which blood tests are usually confirmatory, has a slightly better prognosis than IPF, but its presence worsens the prognosis of the diseases themselves (Castelino and Varga 2010).

Chronic Bronchitis and Bronchiectasis

Chronic bronchitis is defined as chronic cough, usually occurring in the winter months, that lasts for three months or more, occurs in two successive years, and is associated with the production of phlegm.

Acute exacerbations of COPD are more common in patients with chronic bronchitis and are commonly associated with bacterial infections in the bronchi (GOLD 2014). Because exacerbations are thought to lead to more rapid loss of lung function and progression of COPD, preventing them is an important goal of COPD management (Vestbo and Hogg 2006).

However, the symptoms of chronic bronchitis are nonspecific, meaning that other lung conditions, particularly asthma and bronchiectasis, may present with similar symptoms. Inhalation of irritants in outdoor and indoor air pollution (Ehrlich and others 2004; Holland and Reid 1965; Jindal and others 2006) and in the workplace may also produce similar symptoms (Blanc and Torén 2007; Ehrlich and others 2004). There is little evidence that chronic bronchitis not associated with advanced COPD is associated with increased mortality (Peto and others 1983).

In bronchiectasis, increased sputum production is commonly associated with chronic bacterial colonization of the abnormal airways by one or more varieties of pathogenic organism. Infective flare-ups are common, often as a result of the appearance of more virulent organisms, and are marked by an increase in the volume or change in the color of sputum, with or without systemic features of infection, such as malaise and a temperature. The pathology in bronchiectasis involves local thinning and weakening of the bronchial wall, leading to areas of dilatation. In addition, the chronic infection leads to scarring of bronchi beyond the dilated areas that may cause airflow obstruction resembling COPD. Likewise, weakened collapsible bronchi and damage to the lining of bronchi result in ineffective cough and clearance of secretions, favoring persistence and recurrence of infections. Bronchiectasis has become less common in HICs, but remains common in LMICs because of the continuing burden of infectious diseases and lung infections—tuberculosis, human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), pertussis, measles, and adenoviral infections—particularly those occurring in childhood. Other factors, such as malnutrition, that compromise the immune system also play a role (Chalmers, Aliberti, and Blasi 2015).

PRIMARY PREVENTION OF CHRONIC LUNG DISEASES

The clear association between respiratory mortality and socioeconomic conditions strongly suggests that poverty reduction will lead to a lowering of the burden from respiratory disease (Burney and others 2015), although the mechanisms are unknown. The most important specific measure for primary prevention of COPD is smoking cessation, including the reduction of exposure to environmental tobacco smoke, addressed in chapter 4 of this volume (Roy and others 2017) (see box 15.1). Improved prevention and management of tuberculosis are also likely to reduce the prevalence of chronic airway obstruction significantly in some regions, as will improvement of work environments. Other preventive measures for airflow obstruction are less well established; the use of cleaner fuels or improved biomass stoves is expected to reduce at least the symptoms of chronic respiratory diseases.

There is little evidence on the causes of low lung volume (low FVC) or on how low FVC may be prevented. It is reasonable to speculate that improving birth weights through dietary measures and supplements for mothers or children (or both) might be beneficial. Encouraging mothers not to smoke during pregnancy might also be effective. Current large-scale trials of the reduction of biomass exposure will quantify the benefits to be derived from this effort.

The primary prevention of chronic bronchitis also involves reducing the use of tobacco products and exposure to air pollutants. For bronchiectasis, the main strategy is to prevent the spread of infection either by prophylactic treatment (for HIV/AIDS in newborns) or immunization against tuberculosis, measles, and pertussis, in combination with adequate and prompt treatment of infections. Annual influenza and five-yearly polyvalent pneumococcal vaccination may reduce serious morbidity in persons at risk of pneumonia, including the elderly and persons with chronic heart, lung, renal, or liver disease. The role of smoking in increasing the risk of most pulmonary infections, including tuberculosis, provides further grounds for public health measures to target this addiction.

Box 15.1

Common Preventable Causes of Chronic Airflow Obstruction

- Stronger evidence of link to COPD
  - Smoking
  - Tuberculosis
  - Occupational exposure.
- Weaker evidence of link to COPD
  - Indoor air pollution
  - Outdoor air pollution
  - Diet high in oxidants, low in antioxidant content.

PRINCIPLES OF CARE

The aims of disease management for patients with chronic respiratory disease vary according to the nature and stage of the disease. Principal objectives in all cases are early detection to limit the progression and severity of disease, and implementation of secondary preventive measures. Early identification of persons susceptible to the effects of harmful exposures permits a more targeted approach to risk reduction and may be relevant to their family members, for example, by identifying persons with rare genetic conditions that render them susceptible to developing emphysema. At-risk persons need to be given clear instructions on how to avoid potentially harmful smoke and other pollutants.

Proposed treatments need to be evaluated for their efficacy, acceptability, effectiveness, value for money, and scalability (box 15.2). The attributes of an intervention or treatment are not necessarily the same in all environments; most research on the treatment of lung diseases has been performed in HICs, and recommendations may not be applicable in other settings. Nevertheless, the evidence from HICs may be the only evidence available.

Box 15.2

Principles of Care

- *Efficacy of the treatment.* Efficacy is the ability of the treatment to achieve an objective under experimental conditions. Efficacy is best tested in randomized controlled trials (RCTs); the findings may be combined in systematic reviews to arrive at more reliable assessments from which recommendations may be made. A regularly updated source of such reviews can be found at http://www.cochranelibrary.com/app/content/browse/page/?context=topic/Lungs%20%26%20airways. Even this evidence, however, is limited by several factors: the context in which the trials have been conducted; the selection of patients, which is generally more restricted than the use of the treatment in practice; the heterogeneity of patients, who may not all have the same response to treatment; and the selection of the medication with which the medication being studied has been compared. These limitations are particularly relevant to lung diseases in low- and middle-income countries, where few RCTs have been performed and results from high-income countries do not necessarily apply.
- *Effectiveness of the impact of the intervention on a population*. Efficacious remedies may not be used because they are unavailable, unaffordable, or unacceptable to the patients, or they may be prescribed or used inappropriately. Inhaled drugs have a very good ratio of efficacy to side effects. However, acceptability of the inhalation route for treatment delivery is a barrier in some countries; adherence is poor unless there is a concerted effort to promote this form of treatment. Other barriers to use include high costs relative to other treatments; fear of taking corticosteroids; diverse cultural views about treatment of disease; and poor inhaler technique, particularly with pressurized metered dose inhalers, which require coordination of actuation with inhalation (GINA 2014; Masoli and others 2004).
- *Value for money*. Value for money is a comparative judgment generally made by the party paying for the treatment—patients, health authorities, or third-party payers. It involves comparing the relative benefit from the treatment to the benefit that could be derived from all other uses of the available resources. These judgments are not easily transferred from one person or one country to another, and relative costs and available resources may vary markedly.
- *Scalability.* Scalability is the ability to provide a good service to the whole population. Scalability requires simple algorithms (care pathways) to guide the assessment and treatment of patients (Graham and others 2006), access to quality-assured and affordable essential medicines, and inclusion of algorithms in guidelines customized both for the end users (primary care physicians, nurses) and for practice settings (country, facility, human and health resources, prevalent diseases, and health needs) (Ottmani and others 2005).

MANAGEMENT OF CHRONIC LUNG DISEASES

Every effort should be made to reduce all harmful exposures linked to any respiratory disease: tobacco, occupational dusts, and indoor and outdoor pollution. The availability of nicotine replacement therapy is beneficial.

Asthma

Despite the development of many regional and international asthma guidelines that have reduced the burden of disease and death in most countries (Haahtela and others 2006), the level of asthma control is poor in a large proportion of patients in other regions (Ayuk and others 2014; Masoli and others 2004; Price, Fletcher, and van der Molen 2014; Vietri, Burslem, and Su 2014; Zemedkun, Woldemichael, and Tefera 2014). The success in reducing asthma-related death rates in HICs has highlighted the disparity with LMICs.

Diagnosis

Asthma as a heterogeneous disease, usually characterized by chronic airway inflammation and its diagnosis, involves the recognition of characteristic symptoms of periodic respiratory airflow obstruction. The Global Initiative for Asthma (GINA) recommends that the clinical diagnosis should in all cases be confirmed by measurements of reversible airflow at some time, either in the past or currently. Characteristic symptoms are wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity and are relieved, at least partially, by use of a rapid-acting inhaled bronchodilator (GINA 2014). Heterogeneity refers to the varying patterns of disease with respect to onset, time course (Martinez and others 1995), associations with allergic diseases, and severity (Boudier and others 2013). This heterogeneity has important implications for selection of treatment, particularly in severe asthma.

A multidimensional view of asthma that aids diagnosis, assessment, and therapy has been proposed (Gibson, McDonald, and Marks 2010). This multidimensionality includes airway pathology, symptoms, lung function abnormalities, body mass and nutrition, gas exchange abnormalities, exercise capacity, and comorbidity. Other features that may be present are variability of symptoms from day to day and from season to season, onset during early childhood, almost immediate relief from the use of a short-acting bronchodilator, and periods when symptoms disappear, particularly as associated with a trial of inhaled corticosteroids.

Airflow limitation is demonstrated by the use of peak flow meters or spirometers, which measure airflow during forced expiration either as peak expiratory flow or FEV_1 (GINA 2014). These measures are compared with the predicted value for the patient's gender, age, and height. Measurements taken before and after a dose (four puffs are recommended) of a short-acting beta2-agonist confirms reversible airflow limitation, which should be interpreted in the context of the syndromic diagnosis. The pathophysiology of asthma in most cases involves hyperresponsiveness of airway smooth muscle and bronchospasm. Several other respiratory conditions may present with some of these features, and these conditions vary according to the patient's age. The use of alternative diagnostic terms like *recurrent bronchitis* or *wheezy bronchitis* may delay diagnosis and appropriate treatment (Speight, Lee, and Hey 1983).

Assessment

Proper management of the disease involves assessing both day-to-day control (also called *impairment*) and the likelihood of longer-term problems, including asthma exacerbations (also referred to as *risk*) (GINA 2014; National Asthma Education and Prevention Program 2007).

Satisfactory control of asthma symptoms (day-to-day control) is defined as infrequent symptoms during the day (fewer than twice a week) and infrequent need for a short-acting beta2-agonist to relieve symptoms (fewer than twice a week), absence of any night waking due to asthma symptoms, and the achievement of normal or near-normal lung function (if measured). These measures are combined in a single score, and the asthma is described as controlled, partly controlled, or uncontrolled.

A second component of satisfactory asthma control (also called future risk, because these features are usually the result of ongoing poor asthma symptom control, or complications of treatment) includes the following: freedom from attacks of asthma (exacerbations) that require emergency treatment (usually with oral corticosteroids and administration of additional bronchodilators); chronically reduced or declining lung function; and the side-effects caused by long-term or repeated short courses of oral or systemic corticosteroids, a common situation in LMICs without access to safer but more costly asthma medications.

There has been intense research interest in finding simple and accurate ways of measuring predictors of response to therapy to assist in targeting therapy most appropriately, as well as response to therapy to evaluate success. Measurement of the fraction of nitric oxide in exhaled breath (Powell and others 2011),

sputum (Siva and others 2007), and blood eosinophils (Bafadhel and others 2012) are the most promising predictors of response to inhaled corticosteroids and new biologicals such as anti-interleukin-5.

Further implementation research on biomarker-based targeted approaches to therapy for asthma is ongoing. Biomarkers have limited value in diagnosing asthma in routine practice, but they are used in specialized centers. The limited availability and high cost of these tests and of the targeted treatments will restrict their use, even in severe asthma (Chung and others 2014). The great majority of patients with asthma are adequately diagnosed and managed using predominantly symptom-based clinical algorithms that target asthma control alone (GINA 2014).

Pharmacological Management

Control-based asthma management, as recommended in the GINA strategy, is a stepwise approach in which treatment is escalated and de-escalated to establish the lowest level of treatment intensity that maintains symptom control with the absence of asthma attacks (exacerbations). Satisfactory asthma control is defined as infrequent symptoms and need for a short-acting beta2-agonist during the day (fewer than twice per week), night waking due to asthma symptoms, the achievement of normal or near normal lung function (if measured), and freedom from attacks of asthma (exacerbations) that require emergency treatment (usually with oral corticosteroids and administration of additional bronchodilators).

In the GINA strategy, Treatment Step 1 is as-needed use of a rapid- and short-acting beta2-agonist (for example, salbutamol) alone. For persisting symptoms and to reduce exacerbation risk, Step 2 is the addition of regular (once or twice daily) low-dose inhaled corticosteroids *or* leukotriene receptor antagonists. If symptom control is not achieved or exacerbations recur, the next step (Step 3) involves an increase in the dose of inhaled corticosteroids to either a medium dose (the preferred step in children) or a switch to once- or twice-daily use of the combination of a low-dose inhaled corticosteroid and long acting beta2-agonist (for example, formoterol). If this treatment fails to achieve satisfactory symptom control, the next step (Step 4) involves increasing to a medium- or high-dose inhaled corticosteroid combined with a long-acting beta2-agonist. At Step 4, the addition of other controller medications is considered. These include tiotropium (a long-acting inhaled anticholinergic, previously used only for COPD) and theophylline. For patients being considered for Step 4 treatments, referral to a specialist in asthma management is recommended. In Step 5, options include tiotropium, a daily dose of oral corticosteroids (adjusted to the lowest dose that maintains freedom from exacerbations and maximal achievable daily freedom from symptoms), anti-immunoglobulin E therapy (administered as a monthly injection), or the biological agent anti-interleukin-5 (anti-IL5), recently approved for use in severe asthma.

Additional measures are recommended before escalating treatment:

- Check both adherence and inhaler technique
- Treat or avoid modifiable risk or exacerbating factors
- Manage any side effects of treatment.

Long-acting beta2-agonist therapy should never be used without inhaled corticosteroid in patients with asthma; this mode of treatment has been associated with increased risk of death (Durham and others 1999). Only inhaled corticosteroid alone or inhaled corticosteroid plus long-acting beta2-agonist combination inhalers should be prescribed for patients with asthma (U.S. FDA 2010). Relatively low-cost generic versions of all of these classes of drugs are available.

Barriers to Care

The efficacy and safety of inhaled corticosteroids in the management of patients with asthma is well established (Adams, Bestall, and Jones 2009; Adams and others 2008; Adams and others 2009). The use of inhaled corticosteroids is associated with reduced risk of asthma-related death (Suissa and others 2000).

However, many barriers to effective implementation of treatment result in suboptimal outcomes. The most significant barrier in LMICs is access to inhaled corticosteroids, usually because of lack of affordability of the medication (GINA 2014). The ratio of inhaled corticosteroid to rescue inhaler use (bronchodilator) has a strong inverse correlation with hospitalizations for asthma attacks and asthma mortality. The higher the population coverage with inhaled corticosteroid, the lower the asthma morbidity (Phui, Tan, and Lim 2008). The next most important barrier is patient nonadherence to controller treatments, a factor shared with other chronic diseases that require regular daily treatment. Other barriers include delayed diagnosis, ineffective patient education, poor inhaler technique, low expectations of control, and lack of appreciation of inadequate control by physicians and patients. Other barriers are cultural values, preferences, and priorities.

Health system barriers include poor training of health care workers, lack of availability of quality-controlled products, and lack of affordability (Aït-Khaled and others 2000). If good-quality medication is locally available and affordable, the major barrier is the need for patients to take this medication using either inhaled dry powder

or pressurized inhalers with spacers. Poor inhalation technique reduces the efficacy of the medication; poor adherence results in suboptimal control of the disease.

In general, regular follow-up by health care workers may represent the most cost-effective way to improve adherence and ensure correct inhaler techniques. The Finnish asthma program has shown that a community approach to setting up a network of support for practitioners may be a very cost-effective way to improve asthma control (Erhola and others 2003; GINA 2014; Haahtela and others 2001; Haahtela and others 2006; Kauppi and others 2013).

Many asthma educational programs have been developed by national health agencies, such as the Finnish Asthma Program; by individual hospitals; and by patient organizations and nongovernmental organizations. There is no doubt that a combined effort in diagnosis and early use of and easy access to anti-inflammatory therapy, along with periodic assessment of asthma control, will reduce asthma-related morbidity and mortality. Despite the best care, however, approximately 5–10 percent of patients still have significant symptomatic asthma. Alternative approaches to managing these patients, who are responsible for a substantial burden of costs and poor outcomes, are needed (Bousquet and others 2010; Chung and others 2014).

Chronic Airway Obstruction

Diagnosis

COPD typically presents in a person older than age 40 years with breathlessness on exertion that is persistent and progressive. Wheezing and chest tightness and an intermittent or persistent cough that may be associated with the production of sputum may also be present (GOLD 2014). Exacerbations—that is, episodes of worsening of symptoms (breathlessness, cough, or sputum production) beyond the normal day-to-day variation—are an important feature of the history of chronic airway obstruction. The diagnosis is confirmed by spirometry and is defined as FEV_1/FVC ratio below the lower limit of normal following inhalation of a short-acting bronchodilator. This definition of normal is specific to a given age, gender, and height; however, because almost all spirometers can be programmed to show the normal value, the lower limit of normal should be used to define the presence of an abnormality rather than the fixed cutoff of 70 percent.

Not all primary care facilities have access to spirometry, and a peak flow meter can be used to exclude the diagnosis with reasonable accuracy. Moderate obstruction is unlikely if the prebronchodilator peak expiratory flow rate is greater than 2.2 liters per second per square meter (l/sec/m^2); severe disease is unlikely if it is greater than 1.8 l/sec/m^2 postbronchodilator or 1.3 l/sec/m^2 prebronchodilator (Jithoo and others 2013).

Peak flow meters are inexpensive and should be widely available. Spirometers are more expensive, but at least the cheaper of the spirometers need to be available for secondary care. The main limitation of spirometers is lack of training in the use and interpretation of findings.

Clinical Course and Management

Patients with COPD generally experience a slow but progressive cycle of worsening exertional dyspnea, which leads to lack of exercise and muscle deconditioning and reduces both work capacity and quality of life. Exercise programs can, to some extent, slow this cycle, improve effort tolerance, relieve dyspnea and fatigue, and improve quality of life (Lacasse and others 2006). Such programs do not need to be expensive or complex; they are best incorporated into a lifestyle of regular exercise four or more times a week, involving both endurance and muscle strengthening (Iepsen and others 2015). A simple physical activity enhancement program using pedometers can effectively improve physical activity level and quality of life in COPD patients in low-resource settings (Mendoza and others 2015). Aerobic exercise training also reduces disease exacerbations (Güell and others 2000).

Some patients with severe COPD, but not necessarily in respiratory failure, lose body weight. This weight loss is not entirely explained by reduced dietary intake and relates to the systemic effects of chronic lung disease and to deconditioning and loss of muscle mass. This process has an impact on functional ability and quality of life and is associated with increased mortality. Nutritional supplements, coupled with an exercise program, can improve but not reverse this process; they can increase body weight, respiratory muscle strength, walking ability, and quality of life (Ferreira and others 2009). Anabolic steroids have no lasting effect (Pan and others 2014).

For hypoxemic patients with COPD, the long-term use of supplemental oxygen improves survival (Medical Research Council Working Party 1981) and may improve quality of life (Eaton and others 2002). Long-term domiciliary oxygen therapy at a flow rate determined by measurement of blood oxygen saturation may delay the onset of pulmonary hypertension. Its benefit for chronic pulmonary diseases other than COPD has not been demonstrated (Jindal and Agarwal 2012). This therapy should be used for a minimum of 12 hours per day, and it is usually restricted to patients with COPD who have stopped smoking. Ambulatory

oxygen therapy, even if it does not improve survival, facilitates independence, lessens restrictions on physical and social activities, and improves quality of life.

Annual influenza vaccination reduces the incidence of exacerbations, particularly those due to influenza virus, and is recommended for patients with COPD (Poole and others 2006). Although it is not effective against the majority of viruses that cause upper respiratory tract infections, vaccination may reduce morbidity and mortality in these susceptible patients during the annual influenza season. Most of the exacerbations of asthma, especially in children, and COPD are precipitated by a viral upper respiratory tract infection and are accompanied by secondary bacterial bronchial infection. Rhinoviruses, for which no vaccine is available, are the most common viruses responsible for these events; antibiotics are indicated for the bacterial component and when purulent sputum becomes evident (Poole and others 2006). Pneumococcal vaccines are effective in preventing the more severe forms of infection caused by the pneumococcus organism, the most important cause of pneumonia in patients of all ages (Walters and others 2010). Five-yearly administration of polyvalent pneumococcal vaccine is advised for patients with chronic lung disease (Walters and others 2010).

Common comorbid conditions, including heart disease, diabetes, cancer, lower respiratory tract infections, musculoskeletal conditions, and psychiatric disorders, should be treated or controlled to improve outcomes in patients with chronic respiratory disease (Gershon and others 2015).

Pharmacological Management of Stable Disease

Most patients with COPD respond to inhaled short-acting bronchodilators, which are the first line of treatment for symptomatic disease and provide temporary relief of symptoms in most people. Two pharmacological classes of short-acting bronchodilators are available: beta2-agonists and anti-muscarinics. Neither class has a clear advantage (Chong, Karner, and Poole 2012). They may be given either alone or in combination; combination inhalers containing both are available. They are generally administered for use as needed; if symptoms are more persistent, they are administered for use every four to six hours. Their duration of action is less than six hours, which explains their failure to improve patients' quality of life or prevent COPD exacerbations.

Inhaled long-acting beta2-agonists (LABAs) (Kew, Mavergames, and Walters 2013) or long-acting muscarinic antagonists (Karner, Chong, and Poole 2014) are taken once or twice daily and provide sustained bronchodilation. They are recommended for patients with persistent daily symptoms that limit activity, especially those who have experienced at least one COPD exacerbation in the past year. Used alone or in combination, they have been shown to result in sustained bronchodilation, improved symptoms and quality of life, reduced activity limitation, improved endurance for rehabilitation programs, and reduced exacerbations. A short-acting beta2-agonist or short-acting muscarinic antagonist is usually provided for as-needed use. Long-acting formulations are generally well tolerated and are recommended when symptoms are not adequately controlled with inhaled short-acting beta2-agonists.

Short-acting bronchodilators, taken regularly or as required, are cheaper and more widely available; long-acting bronchodilators, taken once or twice daily, are generally more convenient and provide more sustained benefit (GOLD 2014). The U.S. Food and Drug Administration has expressed concern about the occurrence of severe exacerbations by some patients using LABAs (U.S. FDA 2010). This concern seems to be limited to patients who take this class of medication without inhaled corticosteroids.

Oral beta2-agonists and oral theophylline are cheaper alternatives to inhaled bronchodilators. However, they have more systemic side effects and are less effective than inhaled medications. Accordingly, they are not recommended.

The use of inhaled corticosteroids in patients with COPD is controversial. Although these agents are not as effective for COPD as for asthma, they do reduce the frequency of exacerbations in people with a history of frequent exacerbations and severe disease; they also reduce the rate of decline in quality of life (Yang and others 2012). They have not been shown to have any effect on decline in lung function or mortality (GOLD 2014). Their use in COPD has been associated with an increased risk of pneumonia, leading to caution except when specifically indicated (Suissa and others 2013). High doses are contraindicated because the risk of pneumonia is dose related. Other side effects include candidiasis, skin bruising, cataracts, and possibly reactivation of previous pulmonary tuberculosis.

Several combination inhaler devices are available that contain either two long-acting bronchodilators (beta2-adrenergic agonists and muscarinic antagonists) or a long-acting bronchodilator and an inhaled steroid. The effect of these combination inhalers is probably similar to that of the addition of their individual components, but a single inhaler is generally more convenient and may lead to enhanced adherence to treatment regimens.

Evidence about the effectiveness of long-term oral corticosteroids in people with stable chronic airway obstruction is lacking. Their adverse effects, including myopathy, are well established; they are probably best avoided, if possible, or otherwise administered in the smallest feasible dose.

Management of Exacerbations

First-line management of exacerbations of COPD includes the use of repeated inhaled beta2-agonists by the most efficient route; supplemental oxygen if the patient is hypoxemic (the presence of cyanosis, preferably confirmed by oximeter); and either oral corticosteroids or antibiotics, or both. Administration of systemic corticosteroids (usually oral) to patients presenting with acute exacerbations of COPD reduces the risk of treatment failure and early relapse, causes more rapid improvement in lung function (FEV_1), and is associated with shorter length of hospital stay (Walters and others 2014). However, it is also associated with an increased risk of adverse effects (Walters and others 2014). Administration of antibiotics to patients with acute exacerbations of COPD probably reduces the risk of treatment failure; the evidence is strongest for people with severe exacerbations requiring hospitalization (Vollenweider and others 2012).

Supplemental oxygen therapy should be administered to patients with acute exacerbations of COPD who are hypoxemic with low-flow (1–2 liters per minute) oxygen administered via nasal cannulas. In patients with acute or acute-on-chronic respiratory failure (low blood oxygen content) due to an acute exacerbation of COPD, the administration of noninvasive positive pressure ventilation, also known as bi-level positive airway pressure, via a nasal or face mask reduces length of hospital stay, avoids the need for intubation and invasive mechanical ventilation, and may improve survival (Ram and others 2009).

Self-management with prescription drugs to be taken in the event of a subsequent exacerbation reduces the delay in commencing treatment and may reduce the risk of hospitalization. Active rehabilitation following hospitalization reduces mortality and rehospitalization. Methylxanthines are not recommended (GOLD 2014).

Idiopathic Low FVC

There is no recognized treatment for patients with idiopathic low FVC, but careful assessment should be made for comorbidities, including diabetes and cardiovascular disease. Treatment options may be available for patients with low FVC associated with the conditions identified in the next section.

Restrictive and Fibrosing Lung Diseases

Diagnosis

The diagnosis of interstitial lung diseases is generally made following referral to specialists. However, the diagnosis is frequently delayed for several months, and patients are misdiagnosed and wrongly treated for congestive cardiac failure, pneumonia, asthma, COPD, or tuberculosis. The most important clues to the correct diagnosis are a typical chest roentgenogram and the presence of inspiratory crackles and clubbing.

Owing to their rarity, no strategy for screening in the general population is warranted except in populations with a higher risk of developing specific forms of fibrosing lung diseases, such as workers exposed to inhaled agents (fibrogenic dusts such as asbestos or silica or a variety of organic antigens). These categories of worker should be reviewed periodically by radiography with or without spirometric studies. Patients with rheumatoid arthritis, scleroderma, systemic lupus erythematosus, mixed connective tissue disease, and dermatomyositis or polymyositis are also at risk, and their respiratory status should be reviewed regularly by their physicians. Lung involvement in these diseases often dominates the clinical course of the disease and may be fatal.

Treatment

General support measures are appropriate. Reducing or avoiding further exposure to the offending agents in secondary fibrotic lung disease, such as hypersensitivity pneumonitis or pneumoconiosis, is important. The presence of gastroesophageal reflux should be considered in all patients, and appropriate investigations performed; if present, the condition should be treated. The presence of gastroesophageal reflux leads to faster deterioration in lung function and produces more respiratory symptoms (Raghu 2013). Effective treatment of gastroesophageal reflux is possible even in low-resource settings.

No treatment for IPF has improved survival or quality of life sufficiently to be recommended widely in individuals with active and progressive disease. Several drugs and combinations of drugs, predominantly immunosuppressants and corticosteroids, have been used unsuccessfully to treat IPF (Davies, Richeldi, and Walters 2003; Richeldi 2012). Although pirfenidone has not demonstrated a reduction in mortality, it may slow the decline in lung function (FVC, diffusing capacity of carbon monoxide [DL_{CO}], or six-minute walking distance) (Azuma and others 2005; Noble and others 2011; Spagnolo and others 2010; Taniguchi and others 2010). However, its use is associated with significant side effects (Jiang and others 2012). Other drugs investigated in randomized

controlled trials in IPF patients include cotrimoxazole (Shulgina and others 2013), sildenafil (preserves exercise capacity in patients with right-ventricular hypertrophy or systolic dysfunction [Han and others 2013]), and high-dose tyrosine-kinase inhibitor (nintedanib) (Richeldi and others 2011). Confirmation of these findings in other trials is awaited. The more specialized medications are unlikely to be widely available in low-resource settings or outside of third-level facilities.

Exacerbations of IPF have many causes, such as pulmonary thromboembolism, respiratory infection, and heart failure; an idiopathic acute exacerbation has been described, consisting of diffuse alveolar damage. In general, acute exacerbations of IPF are treated with antibiotics, systemic corticosteroids, and, at times, immunosuppressive drugs, although the prognosis remains poor despite these measures (Agarwal and Jindal 2008).

Hypersensitivity pneumonitis (for example, bird fancier's or pigeon-breeder's lung) generally responds to antigen avoidance, but corticosteroids are recommended for highly symptomatic patients with important functional and radiologic abnormalities. Some individuals develop severe fibrosis.

In patients with progressive systemic sclerosis with deteriorating lung function and high-resolution computed tomography abnormalities suggesting inflammation, a modest response to cyclophosphamide was found after one year of treatment, although with significant toxicity (Tashkin and others 2006). This benefit had largely waned at the second year of follow-up (Khanna and others 2007). Patients with progressive interstitial lung disease in rheumatoid arthritis or systemic lupus erythematosus may warrant treatment with corticosteroids, with or without immunosuppressive drugs, although there is little evidence from clinical trials to support the use of this therapy.

Patients with advanced disease or with more aggressive IPF require evaluation for lung transplantation.

Bronchiectasis

Evidence-based guidelines for the management of bronchiectasis have been prepared for HICs (Chang and others 2010; Hill and others 2011), but the quality of the available evidence is low. Management is directed to improving mucus clearance and preventing and treating infections to limit the long-term consequences of repeated episodes of lower respiratory tract infections.

Limited evidence exists for nonpharmacological interventions. Inspiratory muscle training (Bradley, Moran, and Greenstone 2002) is moderately helpful; airway clearance techniques (Lee, Burge, and Holland 2013) are safe and improve quality of life. Moderate evidence supports the use of pneumococcal vaccine (Chang and others 2009) in chronic lung diseases, including bronchiectasis. However, no evidence is available to indicate that influenza vaccine is beneficial, but this void may reflect the small size of studies (Chang, Morris, and Chang 2007).

Inhalation of nebulized mannitol increases the time between exacerbations (Hart and others 2014); mucolytics, such as acetylcysteine, that reduce the tenacity of sputum (Wilkinson and others 2014) may be helpful in conjunction with other therapies. Prolonged antibiotics, particularly macrolides, may be beneficial in reducing purulent sputum and preventing episodes of clinical infection, possibly through their effect on local defense mechanisms rather than their antibiotic properties (Evans, Bara, and Greenstone 2007). Their long-term or even intermittent use is, however, associated with the development of bacterial resistance to antibiotics and colonization of the bronchi with a sequence of more virulent treatment-sensitive organisms like *Moraxella catarrhalis* and streptococcal strains, through *Haemophilus influenzae*, then *Staphylococcus aureus*, and finally, less pathogenic but relatively treatment-resistant organisms, such as *Pseudomonas aeruginosa*. This march of organisms can be reduced by using antibiotics judiciously and using principles and regimens recommended for patients with cystic fibrosis (Chalmers, Aliberti, and Blasi 2015).

SYSTEMS AND ORGANIZATION OF CARE

The system of care for patients with respiratory diseases is as important as the treatments. Chronic respiratory diseases are often overlooked or poorly managed in outmoded health systems that focus on treating exacerbations or acute events rather than relying on effective chronic care to prevent such events. Similarly, a reliable source of continuing care and a clear management plan are as important as the correct diagnosis and initial treatment. The plan most appropriate for a given population depends on the access to care and the available resources, but the principles are similar. Effective management programs for patients with chronic lung disease have improved quality of life and exercise tolerance and reduced hospitalizations; the introduction of national programs has been associated with reduced hospitalization, drug costs, and disabilities associated with asthma (Haahtela and others 2006) as well as hospitalizations and disabilities associated with COPD (Pietinalho and others 2007). In LMICs, the Practical Approach to Lung Health has reduced prescribing

costs per patient (Hamzaoui and Ottmani 2012). Costs of medications remain high in many LMICs, often many times the guide price for essential medicines (Beran and others 2015). Where available at or close to the guide price (table 15.2), however, medications are affordable in most places, particularly among those in paid employment where they may reduce absence due to sickness (Burney and others 2008).

Several key issues in planning health services warrant consideration:

- The importance of ensuring continuity of care, particularly with asthma, has been studied extensively and confirmed in HICs and LMICs.
- Integration ensures that the correct treatment is given at the lowest level capable of delivering it effectively and appropriately and that patients are referred promptly to higher levels of care when appropriate. In most cases, staff members with basic training and adequate supervision can provide care for common conditions.
- Financing arrangements vary substantially; patients in poorer countries are more likely to bear the costs of treatment at the point of service. Financial constraints limit the services that can be offered, particularly for chronic diseases; methods of payment may pose separate barriers. Simple insurance schemes that are affordable, whether individual or financed through taxes or payroll levies, help spread the costs across time and risk groups and make it more likely that uptake of services will be continuous; these schemes may reduce overall costs in the long term.
- Selecting appropriate treatments is inevitably a local decision. The affordable care packages and costs of treatments and staff vary. The cost of importing medications may not vary greatly, but the availability of foreign exchange does.
- The purchasing and security of supply of medications are challenging in some LMICs. The costs are often higher, and the quality is often poor, a consequence of underdeveloped and unregulated markets. The provision of inhalers that have the correct specification for good penetration into the airway is technically difficult. If the supply chain does not deliver affordable and high-quality medications on a regular basis without repeated stockouts, effective management of these conditions is impossible.

The World Health Organization (WHO) programs of integrated care for adults can serve as a model for LMICs. An example is Practical Approach to Lung Health, developed by the Stop TB Partnership, which includes care pathways for the diagnosis and management of asthma and COPD alongside those for screening and treating tuberculosis (WHO 2008). The approach has been implemented and audited in many countries and has provided consistent benefits, even achieving cost savings for health systems. Another example is the Integrated Management of Adolescent and Adult Illness (IMAI), which describes care pathways for acute and chronic diseases, with a strong focus on integrating patient care with care for HIV/AIDS and tuberculosis. IMAI has been implemented in several countries, but its length and density of recommendations present barriers to its use in poorly

Table 15.2 Guide Price for Medicines Commonly Used in COPD and Asthma

Drug	Dose	Median unit price for buyer (US$)	Typical dosage	Indicative cost per month (US$)
Prednisolone	25 mg	0.039	10 tablets	0.39[a]
Salbutamol	100 mcg inhaler	0.0078	2 puffs qds	1.87
Ipratropium	20 mcg inhaler	0.0328	2 puffs qds	7.87
Beclometasone	50 mcg inhaler	0.0131	2 puffs bd	1.57
	100 mcg inhaler	0.0160	2 puffs bd	1.92
	250 mcg inhaler	0.0170	2 puffs bd	2.04
Budesonide	100 mcg inhaler	0.007	2 puffs bd	0.84
	200 mcg inhaler	0.0272	2 puffs bd	3.26
Salmeterol/fluticasone	25/250 mcg inhaler	0.0568	2 puffs bd	6.82

Source: Data extracted from MSH 2015.
Note: bd = two times a day; COPD = chronic obstructive pulmonary disease; mcg = microgram; mg = milligram; qds = four times a day.
a. Cost per course.

resourced countries. However, it may serve as a useful resource for health departments seeking to develop locally applicable integrated models of care (WHO 2013b). A third example is the WHO package of essential noncommunicable disease interventions for primary health care, which includes evidence-based guidelines on diabetes, chronic respiratory disease, cancer, heart disease, and stroke. Pilot implementation projects are ongoing in several countries (box 15.3; WHO 2013a).

Box 15.3

Case Study: Practical Approach to Lung Health in South Africa/Primary Care 101/Practical Approach to Care Kit

A further example of integrated care is the Practical Approach to Lung Health in South Africa/Primary Care 101/Practical Approach to Care Kit (PALSA/PC101/PACK) program. This program, developed in South Africa, began with a local version of Practical Approach to Lung Health (English and others 2006; English and others 2008). After development and testing, the first version of the guideline and training program, called the Practical Approach to Lung Health in South Africa (PALSA), was revised and expanded. The first revision included the chronic care of patients with HIV/AIDS (PALSA PLUS) (Barton and others 2013; Stein and others 2008).

The second revision included the management of approximately 80 percent of the conditions for which adult patients attend primary care clinics, including asthma, COPD, pneumonia, tuberculosis, hypertension, diabetes, and several other common diseases. This program has been developed for international use as the Practical Approach to Care Kit (PACK); it has been introduced in South Africa and is being piloted in Brazil. Versions of PALSA/PACK have been piloted or implemented in Botswana, Brazil, Malawi, and Mexico (Schull and others 2011; Sodhi and others 2014).

This program is based on the following principles:

- *Integration.* Silo management results in prioritization of some diseases; integration ensures their inclusion, which is particularly important for respiratory diseases that have had a low priority, with little provision of resources. Integration ensures that clinicians are led through processes that consider all relevant contributing or comorbid diseases.
- *Localization.* Integrated guidelines are context specific, designed around locally available resources—personnel, facilities, equipment, medications, and local or national health guidelines and prescribing provisions. In many instances, integrated guidelines help guide policy based on review of the evidence and best-buy principles in each country. Annual updates are essential, especially for disease areas where treatment policies change frequently.
- *Clarity.* Integration seeks to strengthen health services by removing inconsistencies in different guidelines and providing clear recommendations for the levels and tasks of health workers. Clarity optimizes work flows, especially in resource-poor settings with heavy workloads, and facilitates task sharing (Fairall and others 2012; Georgeu and others 2012).
- *Effective training.* Training uses modern adult learning techniques. The guideline serves as the curriculum for case-based, onsite continuing education for nurses and physicians. This training has been introduced in nursing colleges and medical schools, replacing the didactic, lecture-based, offsite training that has a poor record for changing the behavior of clinicians (Stein and others 2008; Zwarenstein and others 2011). The results of these programs have been reported in several papers, including four pragmatic cluster randomized controlled trials. These studies have confirmed consistent improvements in clinician behavior and outcomes, including screening, prescribing, and referral. They have further demonstrated that the approach is highly acceptable to all categories of health teams and that users find it empowering and effective. It has resulted in concurrent improvements in the care of patients with communicable and noncommunicable diseases (Fairall and others 2005), improvements in some health outcomes (Fairall and others 2008; Fairall and others 2010), and more appropriate referrals and reductions in the length and duration of hospital admissions. Reports indicate a dose-response effect of the clinical training, confirming the effectiveness of continuing onsite education.

CONCLUSIONS

LMICs typically have a high burden of disease associated with chronic respiratory conditions, yet the information on which to formulate policy is negligible when compared with the information in HICs. The lack of reliable information is compounded by generally poor infrastructure for commissioning, providing, and monitoring services and training and supporting staff members.

The highest mortality attributed to COPD occurs in South-East Asia. This region has very high age-specific mortality from the condition. An understanding of the nature of the problem is only emerging with the completion of large-scale descriptive surveys with good-quality spirometry. The descriptive epidemiology of chronic respiratory diseases remains sketchy in many low-income areas. The studies in these areas clearly do not replicate findings in the more affluent regions. Extrapolating from high- to low-income contexts is not warranted.

Information on the efficacy and safety of different medications is also largely drawn from studies in HICs. Relatively little information specifically addresses the assessment of these medications in other populations. The lack of clarity on the safety of LABAs in some ethnic groups makes it difficult to optimize health care for these groups.

Infrastructure for effective implementation is inadequate. Health services require a reliable and secure supply of diagnostic services, as well as medications and other treatments, to function well. These elements need to be linked to well-supported staff members with the skills to deploy these services optimally.

Examples of effective primary care and tuberculosis control programs in LMICs provide encouraging evidence. Quality of care—diagnosis, treatment, and appropriate referral to higher levels of care—can be achieved through customized integrated programs that educate, empower, and support frontline clinicians, even in severely resource-constrained settings. Such programs can prompt changes in policies and positive resources necessary for managing these common but currently neglected chronic respiratory diseases.

NOTE

World Bank Income Classifications as of July 2014 are as follows, based on estimates of gross national income (GNI) per capita for 2013:

- Low-income countries (LICs) = US$1,045 or less
- Middle-income countries (MICs) are subdivided:
  (a) lower-middle-income = US$1,046 to US$4,125
  (b) upper-middle-income (UMICs) = US$4,126 to US$12,745
- High-income countries (HICs) = US$12,746 or more.

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