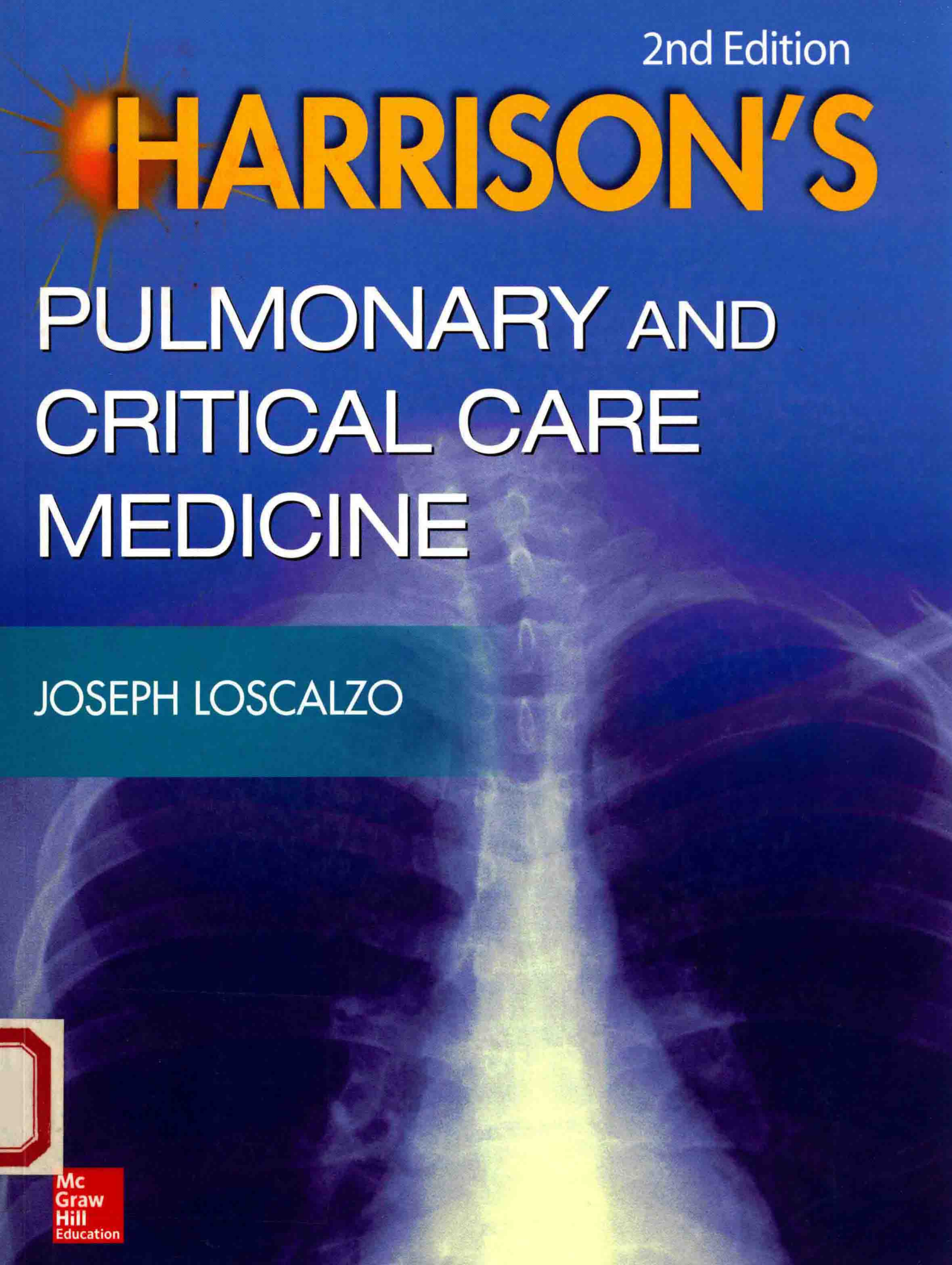
2nd Edition

HARRISON'S

PULMONARY AND CRITICAL CARE MEDICINE

JOSEPH LOSCALZO



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2nd Edition

HARRISON'S™

PULMONARY AND CRITICAL CARE MEDICINE

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Harrison's Pulmonary and Critical Care Medicine, Second Edition

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HARRISON'S™

PULMONARY AND CRITICAL CARE MEDICINE

Derived from Harrison's Principles of Internal Medicine, 18th Edition

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PREFACE

Harrison's Principles of Internal Medicine has been a respected information source for more than 60 years. Over time, the traditional textbook has evolved to meet the needs of internists, family physicians, nurses, and other health care providers. The growing list of *Harrison's* products now includes *Harrison's* for the iPad, *Harrison's Manual of Medicine,* and *Harrison's Online*. This book, *Harrison's Pulmonary and Critical Care Medicine,* now in its second edition, is a compilation of chapters related to respiratory disorders, respiratory diseases, general approach to the critically ill patient, common critical illnesses and syndromes, and disorders complicating critical illnesses and their management.

Our readers consistently note the sophistication of the material in the specialty sections of *Harrison's*. Our goal was to bring this information to our audience in a more compact and usable form. Because the topic is more focused, it is possible to enhance the presentation of the material by enlarging the text and the tables. We have also included a Review and Self-Assessment section that includes questions and answers to provoke reflection and to provide additional teaching points.

Pulmonary diseases are major contributors to morbidity and mortality in the general population. Although advances in the diagnosis and treatment of many common pulmonary disorders have improved the lives of patients, these complex illnesses continue to affect a large segment of the global population. The impact of cigarette smoking cannot be underestimated in this regard, especially given the growing prevalence of tobacco use in the developing world. Pulmonary medicine is, therefore, of critical global importance to the field of internal medicine.

Pulmonary medicine is a growing subspecialty and includes a number of areas of disease focus, including reactive airways diseases, chronic obstructive lung disease, environmental lung diseases, and interstitial lung diseases. Furthermore, pulmonary medicine is linked to the field of critical care medicine, both cognitively and as a standard arm of the pulmonary fellowship training programs at most institutions. The breadth of knowledge in critical care medicine extends well beyond the respiratory system, of course, and includes selected areas of cardiology, infectious diseases, nephrology, and hematology. Given the complexity of these disciplines and the crucial role of the internist in guiding the management of patients with chronic lung diseases and in helping to guide the management of patients in the intensive care setting, knowledge of the discipline is essential for competency in the field of internal medicine.

The scientific basis of many pulmonary disorders and intensive care medicine is rapidly expanding. Novel diagnostic and therapeutic approaches, as well as prognostic assessment strategies, populate the published literature with great frequency. Maintaining updated knowledge of these evolving areas is, therefore, essential for the optimal care of patients with lung diseases and critical illness.

In view of the importance of pulmonary and critical care medicine to the field of internal medicine and the speed with which the scientific basis of the discipline is evolving, this sectional was developed. The purpose of this book is to provide the readers with an overview of the field of pulmonary and critical care medicine. To achieve this end, this sectional comprises the key pulmonary and critical care medicine chapters in *Harrison's Principles of Internal Medicine,* 18th edition, contributed by leading experts in the fields. This sectional is designed not only for physicians-in-training, but also for medical students, practicing clinicians, and other health care professionals who seek to maintain adequately updated knowledge of this rapidly advancing field. The editors believe that this book will improve the reader's knowledge of the discipline, as well as highlight its importance to the field of internal medicine.

The first section of the book, "Diagnosis of Respiratory Disorders," provides a systems overview, beginning with approach to the patient with disease of the respiratory system. The integration of pathophysiology with clinical management is a hallmark of *Harrison's,* and can be found throughout each of the subsequent disease-oriented chapters. The book is divided into five main sections that reflect the scope of pulmonary and critical care medicine: (I) Diagnosis of Respiratory Disorders; (II) Diseases of the Respiratory System; (III) General Approach to the Critically Ill Patient; (IV) Common Critical Illnesses and Syndromes; and (V) Disorders Complicating Critical Illnesses and Their Management.

Our access to information through web-based journals and databases is remarkably efficient. Although these sources of information are invaluable, the daunting body of data creates an even greater need for synthesis by experts in the field. Thus, the preparation of these chapters is a special craft that requires the ability to distill core information from the ever-expanding knowledge base. The editors are, therefore, indebted to our authors, a group of internationally recognized authorities who are masters at providing a comprehensive overview while being able to distill a topic into a concise and interesting chapter. We are indebted to our colleagues at McGraw-Hill. Jim Shanahan is a champion for *Harrison's* and these books were impeccably produced by Kim Davis. We hope you will find this book useful in your effort to achieve continuous learning on behalf of your patients

Joseph Loscalzo, MD, PhD

NOTICE

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. The authors and the publisher of this work have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication. However, in view of the possibility of human error or changes in medical sciences, neither the authors nor the publisher nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they disclaim all responsibility for any errors or omissions or for the results obtained from use of the information contained in this work. Readers are encouraged to confirm the information contained herein with other sources. For example and in particular, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this work is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in connection with new or infrequently used drugs.

Review and self-assessment questions and answers were taken from Wiener CM, Brown CD, Hemnes AR (eds). *Harrison's Self-Assessment and Board Review*, 18th ed. New York, McGraw-Hill, 2012, ISBN 978-0-07-177195-5.

The global icons call greater attention to key epidemiologic and clinical differences in the practice of medicine throughout the world.

The genetic icons identify a clinical issue with an explicit genetic relationship.

CONTENTS

SECTION IV

COMMON CRITICAL ILLNESSES AND SYNDROMES

SECTION V

DISORDERS COMPLICATING CRITICAL ILLNESSES AND THEIR MANAGEMENT

SECTION I

DIAGNOSIS OF RESPIRATORY DISORDERS

CHAPTER 1

APPROACH TO THE PATIENT WITH DISEASE OF THE RESPIRATORY SYSTEM

Patricia Kritek ■ Augustine Choi

The majority of diseases of the respiratory system fall into one of three major categories: (1) obstructive lung diseases; (2) restrictive disorders; and (3) abnormalities of the vasculature. Obstructive lung diseases are most common and primarily include disorders of the airways such as asthma, chronic obstructive pulmonary disease (COPD), bronchiectasis, and bronchiolitis. Diseases resulting in restrictive pathophysiology include parenchymal lung diseases, abnormalities of the chest wall and pleura, as well as neuromuscular disease. Disorders of the pulmonary vasculature are not always recognized and include pulmonary embolism, pulmonary hypertension, and pulmonary venoocclusive disease. Although many specific diseases fall into these major categories, both infective and neoplastic processes can affect the respiratory system and may result in myriad pathologic findings, including obstruction, restriction, and pulmonary vascular disease (see Table 1-1).

The majority of respiratory diseases present with abnormal gas exchange. Disorders can also be grouped into the categories of gas exchange abnormalities, including hypoxemic, hypercarbic, or combined impairment. Importantly, many diseases of the lung do not manifest gas exchange abnormalities.

As with the evaluation of most patients, the approach to a patient with disease of the respiratory system begins with a thorough history. A focused physical examination is helpful in further categorizing the specific pathophysiology. Many patients will subsequently undergo pulmonary function testing, chest imaging, blood and sputum analysis, a variety of serologic or microbiologic studies, and diagnostic procedures, such as bronchoscopy. This step-wise approach is discussed in detail later.

HISTORY

DYSPNEA AND COUGH

The cardinal symptoms of respiratory disease are dyspnea and cough (Chaps. 2 and 3). Dyspnea can result from many causes, some of which are not predominantly caused by lung pathology. The words a patient uses to describe breathlessness or shortness of breath can suggest certain etiologies of the dyspnea. Patients with obstructive lung disease often complain of "chest tightness" or "inability to get a deep breath," whereas patients with congestive heart failure more commonly report "air hunger" or a sense of suffocation.

The tempo of onset and duration of a patient's dyspnea are helpful in determining the etiology. Acute shortness of breath is usually associated with sudden physiological changes, such as laryngeal edema, bronchospasm, myocardial infarction, pulmonary embolism, or pneumothorax. Patients with underlying lung disease commonly have progressive shortness of breath or episodic dyspnea. Patients with COPD and idiopathic pulmonary fibrosis (IPF) have a gradual progression of dyspnea on exertion, punctuated by acute exacerbations of shortness of breath. In contrast, most asthmatics have normal breathing the majority of the time and have recurrent episodes of dyspnea usually associated with specific triggers, such as an upper respiratory tract infection or exposure to allergens.

Specific questioning should focus on factors that incite the dyspnea, as well as any intervention that helps resolve the patient's shortness of breath. Of the obstructive lung diseases, asthma is most likely to have specific triggers related to sudden onset of dyspnea, although this can also be true of COPD. Many patients with

TABLE 1-1

CATEGORIES OF RESPIRATORY DISEASE

CATEGORY	EXAMPLES
Obstructive lung disease	Asthma COPD Bronchiectasis Bronchiolitis
Restrictive pathophysiology—parenchymal disease	Idiopathic pulmonary fibrosis (IPF) Asbestosis Desquamative interstitial pneumonitis (DIP) Sarcoidosis
Restrictive pathophysiology—neuromuscular weakness	Amyotrophic lateral sclerosis (ALS) Guillain-Barré syndrome
Restrictive pathophysiology—chest wall/pleural disease	Kyphoscoliosis Ankylosing spondylitis Chronic pleural effusions
Pulmonary vascular disease	Pulmonary embolism Pulmonary arterial hypertension (PAH)
Malignancy	Bronchogenic carcinoma (non-small-cell and small cell) Metastatic disease
Infectious diseases	Pneumonia Bronchitis Tracheitis

Abbreviation: COPD, chronic obstructive pulmonary disease.

lung disease report dyspnea on exertion. It is useful to determine the degree of activity that results in shortness of breath as it gives the clinician a gauge of the patient's degree of disability. Many patients adapt their level of activity to accommodate progressive limitation. For this reason it is important, particularly in older patients, to delineate the activities in which they engage and how they have changed over time. Dyspnea on exertion is often an early symptom of underlying lung or heart disease and warrants a thorough evaluation.

Cough is the other common presenting symptom that generally indicates disease of the respiratory system. The clinician should inquire about the duration of the cough, whether or not it associated with sputum production, and any specific triggers that induce it. Acute cough productive of phlegm is often a symptom of infection of the respiratory system, including processes affecting the upper airway (e.g., sinusitis, tracheitis) as well as the lower airways (e.g., bronchitis, bronchiectasis) and lung parenchyma (e.g., pneumonia). Both the quantity and quality of the sputum, including whether it is blood-streaked or frankly bloody, should be determined. Hemoptysis warrants an evaluation as delineated in Chap. 3.

Chronic cough (defined as persisting for more than 8 weeks) is commonly associated with obstructive lung diseases, particularly asthma and chronic bronchitis, as well as "nonrespiratory" diseases, such as gastroesophageal reflux (GERD) and postnasal drip. Diffuse parenchymal lung diseases, including idiopathic pulmonary fibrosis, frequently present with a persistent, nonproductive cough. As with dyspnea, all causes of cough are not respiratory in origin, and assessment should consider a broad differential, including cardiac and gastrointestinal diseases as well as psychogenic causes.

ADDITIONAL SYMPTOMS

Patients with respiratory disease may complain of wheezing, which is suggestive of airways disease, particularly asthma. Hemoptysis, which must be distinguished from epistaxis or hematemesis, can be a symptom of a variety of lung diseases, including infections of the respiratory tract, bronchogenic carcinoma, and pulmonary embolism. Chest pain or discomfort is also often thought to be respiratory in origin. As the lung parenchyma is not innervated with pain fibers, pain in the chest from respiratory disorders usually results from either diseases of the parietal pleura (e.g., pneumothorax) or pulmonary vascular diseases (e.g., pulmonary hypertension). As many diseases of the lung can result in strain on the right side of the heart, patients may also present with symptoms of cor pulmonale, including abdominal bloating or distention, and pedal edema.

ADDITIONAL HISTORY

A thorough social history is an essential component of the evaluation of patients with respiratory disease. All patients should be asked about current or previous cigarette smoking as this exposure is associated with many diseases of the respiratory system, most notably COPD and bronchogenic lung cancer but also a variety of diffuse parenchymal lung diseases (e.g., desquamative interstitial pneumonitis [DIP] and pulmonary Langerhans cell histiocytosis). For most disorders, the duration and intensity of exposure to cigarette smoke increases the risk of disease. There is growing evidence that "second-hand smoke" is also a risk factor for respiratory tract pathology; for this reason, patients should be asked about parents, spouses, or housemates who smoke. It is becoming less common for patients to be exposed to cigarette smoke on the job, but for older patients, an occupational history should include the potential for heavy cigarette smoke exposure (e.g., flight attendants working prior to prohibition of smoking on airplanes).

Possible inhalational exposures should be explored, including those at the work place (e.g., asbestos, wood

smoke) and those associated with leisure (e.g., pigeon excrement from pet birds, paint fumes) (Chap. 10). Travel predisposes to certain infections of the respiratory tract, most notably the risk of tuberculosis. Potential exposure to fungi found in specific geographic regions or climates (e.g., *Histoplasma capsulatum*) should be explored.

Associated symptoms of fever and chills should raise the suspicion of infective etiologies, both pulmonary and systemic. Some systemic diseases, commonly rheumatologic or autoimmune, present with respiratory tract manifestations. Review of systems should include evaluation for symptoms that suggest undiagnosed rheumatologic disease. These may include joint pain or swelling, rashes, dry eyes, dry mouth, or constitutional symptoms. Additionally, carcinomas from a variety of primary sources commonly metastasize to the lung and cause respiratory symptoms. Finally, therapy for other conditions, including both radiation and medications, can result in diseases of the chest.

PHYSICAL EXAMINATION

The clinician's suspicion for respiratory disease often begins with a patient's vital signs. The respiratory rate is often informative, whether elevated (tachypnea) or depressed (hypopnea). In addition, pulse oximetry should be measured as many patients with respiratory disease will have hypoxemia, either at rest or with exertion.

Simple observation of the patient is informative. Patients with respiratory disease may be in distress, often using accessory muscles of respiration to breathe. Severe kyphoscoliosis can result in restrictive pathophysiology. Inability to complete a sentence in conversation is generally a sign of severe impairment and should result in an expedited evaluation of the patient.

AUSCULTATION

The majority of the manifestations of respiratory disease present with abnormalities of the chest examination. Wheezes suggest airway obstruction and are most commonly a manifestation of asthma. Peribronchial edema in the setting of congestive heart failure, often referred to as "cardiac asthma," can also result in diffuse wheezes as can any other process that causes narrowing of small airways. For this reason, clinicians must take care not to attribute all wheezing to asthma.

Rhonchi are a manifestation of obstruction of medium-sized airways, most often with secretions. In the acute setting, this may be a sign of viral or bacterial bronchitis. Chronic rhonchi suggest bronchiectasis or COPD. Bronchiectasis, or permanent dilation and irregularity of the bronchi, often causes what is referred to as a "musical chest" with a combination of rhonchi, pops, and squeaks. Stridor or a low-pitched, focal inspiratory wheeze usually heard over the neck, is a manifestation of upper airway obstruction and should result in an expedited evaluation of the patient as it can precede complete upper airway obstruction and respiratory failure.

Crackles, or rales, are commonly a sign of alveolar disease. A variety of processes that fill the alveoli with fluid result in crackles. Pneumonia, or infection of the lower respiratory tract and air spaces, may cause crackles. Pulmonary edema, of cardiogenic or noncardiogenic cause, is associated with crackles, generally more prominent at the bases. Interestingly, diseases that result in fibrosis of the interstitium (e.g., IPF) also result in crackles often sounding like Velcro being ripped apart. Although some clinicians make a distinction between "wet" and "dry" crackles, this has not been shown to be a reliable way to differentiate among etiologies of respiratory disease.

One way to help distinguish between crackles associated with alveolar fluid and those associated with interstitial fibrosis is to assess for egophony. Egophony is the auscultation of the sound "AH" instead of "EEE" when a patient phonates "EEE." This change in note is due to abnormal sound transmission through consolidated lung and will be present in pneumonia but not in IPF. Similarly, areas of alveolar filling have increased whispered pectoriloquy as well as transmission of larger airway sounds (i.e., bronchial breath sounds in a lung zone where vesicular breath sounds are expected).

The lack of breath sounds or diminished breath sounds can also help determine the etiology of respiratory disease. Patients with emphysema often have a quiet chest with diffusely decreased breath sounds. A pneumothorax or pleural effusion may present with an area of absent breath sounds, although this is not always the case.

REMAINDER OF CHEST EXAMINATION

In addition to auscultation, percussion of the chest helps distinguish among pathologic processes of the respiratory system. Diseases of the pleural space are often suggested by differences in percussion note. An area of dullness may suggest a pleural effusion, whereas hyperresonance, particularly at the apex, can indicate air in the pleural space (i.e., pneumothorax).

Tactile fremitus will be increased in areas of lung consolidation, such as pneumonia, and decreased with pleural effusion. Decreased diaphragmatic excursion can suggest neuromuscular weakness manifesting as respiratory disease or hyperinflation associated with COPD.

Careful attention should also be paid to the cardiac examination with particular emphasis on signs of right heart failure as it is associated with chronic hypoxemic lung disease and pulmonary vascular disease. The clinician should feel for a right ventricular heave and listen for a prominent P2 component of the second heart sound, as well as a right-sided S4.

OTHER SYSTEMS

Pedal edema, if symmetric, may suggest cor pulmonale, and if asymmetric may be due to deep venous thrombosis and associated pulmonary embolism. Jugular venous distention may also be a sign of volume overload associated with right heart failure. Pulsus paradoxus is an ominous sign in a patient with obstructive lung disease as it is associated with significant negative intrathoracic (pleural) pressures required for ventilation, and impending respiratory failure.

As stated earlier, rheumatologic disease may manifest primarily as lung disease. Owing to this association, particular attention should be paid to joint and skin examination. Clubbing can be found in many lung diseases, including cystic fibrosis, IPF, and lung cancer, although it can also be associated with inflammatory bowel disease or as a congenital finding of no clinical importance. Patients with COPD do not usually have clubbing; thus, this sign should warrant an investigation for second process, most commonly an unrecognized bronchogenic carcinoma, in these patients. Cyanosis is seen in hypoxemic respiratory disorders that result in more than 5 g/dL deoxygenated hemoglobin.

DIAGNOSTIC EVALUATION

The sequence of studies is dictated by the clinician's differential diagnosis determined by the history and physical examination. Acute respiratory symptoms are often evaluated with multiple tests obtained at the same time in order to diagnose any life threatening diseases rapidly (e.g., pulmonary embolism or multilobar pneumonia). In contrast, chronic dyspnea and cough can be evaluated in a more protracted, step-wise fashion.

PULMONARY FUNCTION TESTING

(See also Chap. 6) The initial pulmonary function test obtained is spirometry. This study is used to assess for obstructive pathophysiology as seen in asthma, COPD, and bronchiectasis. A diminished forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) (often defined as less than 70% of predicted value) is diagnostic of obstruction. History as well as further testing can help distinguish among different obstructive diseases. COPD is almost exclusively seen in cigarette smokers. Asthmatics often show an acute response to inhaled bronchodilators (e.g., albuterol). In addition to the measurements of FEV_1 and FVC, the clinician should examine the flow-volume loop. A plateau of the inspiratory or expiratory curves suggests large airway obstruction in extrathoracic and intrathoracic locations, respectively.

Normal spirometry or spirometry with symmetric decreases in FEV_1 and FVC warrants further testing, including lung volume measurement and the diffusion capacity of the lung for carbon monoxide (D_LCO). A total lung capacity (TLC) less than 80% of the predicted value for a patient's age, race, gender, and height defines restrictive pathophysiology. Restriction can result from parenchymal disease, neuromuscular weakness, or chest wall or pleural diseases. Restriction with impaired gas exchange, as indicated by a decreased D_LCO, suggests parenchymal lung disease. Additional testing, such as maximal expiratory pressure (MEP) and maximal inspiratory pressure (MIP), can help diagnose neuromuscular weakness. Normal spirometry, normal lung volumes, and a low D_LCO should prompt further evaluation for pulmonary vascular disease.

Arterial blood gas testing is often also helpful in assessing respiratory disease. Hypoxemia, while usually apparent with pulse oximetry, can be further evaluated with the measurement of arterial PO_2 and the calculation of an alveolar gas and arterial blood oxygen tension difference [$(A\text{-}a)DO_2$]. It should also be noted that at times, most often due to abnormal hemoglobins or non-oxygen hemoglobin-ligand complexes, pulse oximetry can be misleading (such as observed with carboxyhemoglobin). Diseases that cause ventilation-perfusion mismatch or shunt physiology will have an increased $(A\text{-}a)DO_2$ at rest. Arterial blood gas testing also allows for the measurement of arterial PCO_2. Most commonly, acute or chronic obstructive lung disease presents with hypercarbia; however, many diseases of the respiratory system can cause hypercarbia if the resulting increase in work of breathing is greater than that which allows a patient to sustain an adequate minute ventilation.

CHEST IMAGING

(See Chap. 7) Most patients with disease of the respiratory system will undergo imaging of the chest as part of initial evaluation. Clinicians should generally begin with a plain chest radiograph, preferably posterior-anterior (PA) and lateral films. Several findings, including opacities of the parenchyma, blunting of the costophrenic angles, mass lesions, and volume loss, can be very helpful in determining an etiology. It should be noted that many diseases of the respiratory system, particularly those of the airways and pulmonary vasculature, are associated with a normal chest radiograph.

Subsequent computed tomography of the chest (CT scan) is often obtained. The CT scan allows better delineation of parenchymal processes, pleural disease, masses or nodules, and large airways. If administered with contrast, the pulmonary vasculature can be assessed with particular utility for determination of pulmonary emboli. Intravenous contrast also allows lymph nodes to be delineated in greater detail.