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БОЛЕЗНИ ОРГАНОВ ДЫХАНИЯ

Учебно-методическое пособие
для студентов 4 и 6 курсов факультета подготовки специалистов
для зарубежных стран медицинских вузов

PULMONARY DISEASES

The educational methodical work
for 4th and 6th years medical students
of the Faculty of preparation of experts for foreign countries
of medical higher educational institutions

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1. PRESENTATION OF THE PATIENT WITH PULMONARY DISEASE

The patient with a pulmonary problem generally comes to the attention of the clinician for one of two reasons: (1) complaint of a symptom that can be traced to a respiratory cause, or (2) incidental finding of an abnormality on chest radiograph.

Four particularly common and a number of less common symptoms bring the patient with lung disease to the physician: dyspnea (and its variants), cough (with or without sputum production), hemoptysis, and chest pain. Each of these symptoms, to a greater or lesser extent, may result from a non-pulmonary disorder, especially primary cardiac disease. For each symptom, a discussion of some of the important clinical features is followed by the pathophysiologic features and the differential diagnosis.

DYSPNEA

Dyspnea, or shortness of breath, is frequently a difficult symptom for the physician to evaluate because it is such a subjective feeling experienced by the patient. It is perhaps best defined as an uncomfortable sensation (or awareness) of one's own breathing, to which little attention normally is paid. However, the term *dyspnea* probably subsumes several sensations that are qualitatively distinct. As a result, when patients are asked to describe in more detail their sensation of breathlessness, their descriptions tend to fall into three primary categories: (1) air hunger or suffocation, (2) increased effort or work of breathing, and (3) chest tightness.

The differential diagnosis includes a broad range of disorders that result in dyspnea (Table 1.1.). The disorders can be separated into the major categories of *respiratory disease* and *cardiovascular disease*. In addition, dyspnea may be present in conditions associated with *increased respiratory drive,* even in the absence of underlying respiratory or cardiovascular disease, or it may have an *anxiety-related* or *psychosomatic origin*.

Table 1.1 — Differential Diagnosis of Dyspnea

RESPIRATORY DISEASE
Airway disease
    Asthma
    Chronic obstructive lung disease
    Upper airway obstruction
Parenchymal lung disease
    Acute respiratory distress syndrome
    Pneumonia
    Interstitial lung disease
Pulmonary vascular disease
    Pulmonary emboli
Pleural disease
    Pneumothorax

Pleural effusion
«Bellows» disease
    Neuromuscular disease (e.g., polymyositis, myasthenia gravis, Guillain-Barre syndrome)
    Chest wall disease (e.g., kyphoscoliosis)
CARDIOVASCULAR DISEASE
Elevated pulmonary venous pressure
    Left ventricular failure
    Mitral stenosis
Decreased cardiac output
Severe anemia
INCREASED RESPIRATORY DRIVE
Hyperthyroidism
Pregnancy
ANXIETY/PSYCHOSOMATIC ORIGIN

COUGH

Cough is a symptom that everyone has experienced at some point. It is a physiologic mechanism for clearing and protecting the airway and does not necessarily imply disease. Normally, cough is protective against food or other foreign material entering the airway. It also is responsible for aiding in the clearance of secretions produced within the tracheobronchial tree. Generally, mucociliary clearance is adequate to propel secretions upward through the trachea and into the larynx so that the secretions can be removed from the airway and swallowed. However, if the mucociliary clearance mechanism is temporarily damaged or not functioning well, or if the mechanism is overwhelmed by excessive production of secretions, then cough becomes an important additional mechanism for clearing the tracheobronchial tree.

Cough usually is initiated by stimulation of receptors (called *irritant receptors*) at a number of locations. Irritant receptor nerve endings are found primarily in the larynx, trachea, and major bronchi, particularly at points of bifurcation. However, sensory receptors are also located in other parts of the upper airway as well as on the pleura, the diaphragm, and even the pericardium. Irritation of these nerve endings initiates an impulse that travels via afferent nerves (primarily the vagus but also trigeminal, glossopharyngeal, and phrenic) to a poorly defined cough center in the medulla. The efferent signal is carried in the recurrent laryngeal nerve (a branch of the vagus), which controls closure of the glottis, and in phrenic and spinal nerves, which effect contraction of the diaphragm and the expiratory muscles of the chest and abdominal walls. The initial part of the cough sequence is a deep inspiration to a high lung volume, followed by closure of the glottis, contraction of the expiratory muscles, and opening of the glottis. When the glottis suddenly opens, contraction of the expiratory muscles and relaxation of the diaphragm produce an explosive rush of air at high velocity, which transports airway secretions or foreign material out of the tracheobronchial tree.

The major causes of cough are listed in Table 1.2.

Table 1.2 — Differential Diagnosis of Cough

AIRWAY IRRITANTS
Inhaled smoke, dusts, fumes
Aspiration
Gastric contents
Oral secretions
Foreign bodies
Postnasal drip
AIRWAY DISEASE
Upper respiratory tract infection
Postinfectious cough
Acute or chronic bronchitis
Eosinophilic bronchitis
Bronchiectasis
Neoplasm
External compression by node or mass lesion
Reactive airways disease (asthma)
PARENCHYMAL DISEASE
Pneumonia
Lung abscess
Interstitial lung disease
CONGESTIVE HEART FAILURE
MISCELLANEOUS
Drug-induced (angiotensin-converting enzyme inhibitors)

The symptom of cough is generally characterized by whether it is productive or nonproductive of sputum. Virtually any cause of cough may be productive at times of small amounts of clear or mucoid sputum. However, thick yellow or green sputum indicates the presence of numerous leukocytes in the sputum, either neutrophils or eosinophils. Neutrophils may be present with just an inflammatory process of the airways or parenchyma, but they also frequently reflect the presence of a bacterial infection. Specific examples include bacterial bronchitis, bronchiectasis, lung abscess, and pneumonia. Eosinophils, which can be seen after special preparation of the sputum, often occur with bronchial asthma, whether or not an allergic component plays a role, and in the much less common entity of eosinophilic bronchitis. In clinical practice, cough often is divided into three major temporal categories: acute, subacute, or chronic, depending on the duration of the symptom. *Acute cough,* defined by a duration of less than 3 weeks, is most commonly due to an acute viral infection of the respiratory tract, such as the common cold. *Subacute cough* is defined by a duration of 3 to 8 weeks, and *chronic cough* lasts 8 or more weeks. Whereas chronic bronchitis is a particularly frequent cause of cough in smokers, common causes of either subacute or chronic cough in nonsmokers are postnasal drip (also called *upper airway cough syndrome*), gastroesophageal reflux, and asthma. An im-

portant subacute cough is *postinfectious cough* that lasts for more than 3 weeks following an upper respiratory tract infection. It is often due to persistent airway inflammation, postnasal drip, or bronchial hyperresponsiveness (as seen with asthma). In all cases, however, the clinician must keep in mind the broader differential diagnosis of cough outlined in Table 1.2, recognizing that cough may be a marker and the initial presenting symptom of a more serious disease, such as carcinoma of the lung.

HEMOPTYSIS

Hemoptysis is coughing or spitting up blood derived from airways or the lung itself. When the patient complains of coughing or spitting up blood, whether the blood actually originated from the respiratory system is not always apparent. Other sources of blood include the nasopharynx (particularly in the common nosebleed), the mouth (even lip or tongue biting can be mistaken for hemoptysis), and the upper gastrointestinal tract (esophagus, stomach, and duodenum). The patient can often distinguish some of these causes of pseudohemoptysis, but the physician also should search by examination for a mouth or nasopharyngeal source. The major causes of hemoptysis can be divided into three categories based on location: airways, pulmonary parenchyma, and vasculature (Table 1.3).

Table 1.3 — Differential Diagnosis of Hemoptysis

AIRWAY DISEASE
Acute or chronic bronchitis
Bronchiectasis
Bronchogenic carcinoma
Bronchial carcinoid tumor (bronchial adenoma)
Other endobronchial tumors (Kaposi's sarcoma, metastatic carcinoma)
PARENCHYMAL DISEASE
Tuberculosis
Lung abscess
Pneumonia
Mycetoma («fungus ball»)
Miscellaneous
    Goodpasture's syndrome
    Idiopathic pulmonary hemosiderosis
    Wegener's granulomatosis
VASCULAR DISEASE
Pulmonary embolism
Elevated pulmonary venous pressure
    Left ventricular failure
    Mitral stenosis
Vascular malformation
MISCELLANEOUS/RARE CAUSES
Impaired coagulation
Pulmonary endometriosis

CHEST PAIN

Chest pain as a reflection of respiratory system disease does not originate in the lung itself, which is free of sensory pain fibers. When chest pain does occur in this setting, its origin usually is the parietal pleura (lining the inside of the chest wall), the diaphragm, or the mediastinum, each of which has extensive innervation by nerve fibers capable of pain sensation.

For the parietal pleura or the diaphragm, an inflammatory or infiltrating malignant process generally produces the pain. When the diaphragm is involved, the pain commonly is referred to the shoulder. In contrast, pain from the parietal pleura usually is relatively well localized over the area of involvement. Pain involving the pleura or the diaphragm often is worsened on inspiration; in fact, chest pain that is particularly pronounced on inspiration is described as «pleuritic». Inflammation of the parietal pleura producing pain often is secondary to pulmonary embolism or to pneumonia extending to the pleural surface. A pneumothorax may result in acute onset of pleuritic pain, although the mechanism is not clear inasmuch as an acute inflammatory process is unlikely to be involved. Some diseases, particularly connective tissue disorders such as lupus, may result in episodes of pleuritic chest pain from a primary inflammatory process involving the pleura. Inflammation of the parietal pleura as a result of a viral infection (e.g., viral pleurisy) is a common cause of pleuritic chest pain in otherwise healthy individuals. Infiltrating tumor can produce chest pain by affecting the parietal pleura or adjacent soft tissue, bones, or nerves. In the case of malignant mesothelioma, the tumor arises from the pleura itself. In other circumstances, such as lung cancer, the tumor may extend directly to the pleural surface or involve the pleura after bloodborne (hematogenous) metastasis from a distant site. A variety of disorders originating in the mediastinum may result in pain; they may or may not be associated with additional problems in the lung itself.

PHYSICAL EXAMINATION

The most accessible method for evaluating the patient with respiratory disease is the physical examination, which requires only a stethoscope; the eyes, ears, and hands of the examiner; and the examiner's skill in eliciting and recognizing abnormal findings.

Apart from general observation of the patient, precise measurement of the patient's respiratory rate, and interpretation of the patient's pattern of and difficulty with breathing, the examiner relies primarily on palpation and percussion of the chest and auscultation with a stethoscope. *Palpation* is useful for comparing the expansion of the two sides of the chest. The examiner can determine whether the two lungs are expanding symmetrically or if some process is affecting aeration much more on one side than on the other. Palpation of the chest wall also is useful for feeling the

vibrations created by spoken sounds. When the examiner places a hand over an area of lung, vibration normally should be felt as the sound is transmitted to the chest wall. This vibration is called *vocal* or *tactile fremitus.* Some disease processes improve transmission of sound and augment the intensity of the vibration. Other conditions diminish transmission of sound and reduce the intensity of the vibration or eliminate it altogether.

When **percussing** the chest, the examiner notes the quality of sound produced by tapping a finger of one hand against a finger of the opposite hand pressed closely to the patient's chest wall. The principle is similar to that of tapping a surface and judging whether what is underneath is solid or hollow. Normally, percussion of the chest wall overlying air-containing lung gives a resonant sound, whereas percussion over a solid organ such as the liver produces a dull sound. This contrast allows the examiner to detect areas with something other than air-containing lung beneath the chest wall, such as fluid in the pleural space (pleural effusion) or airless (consolidated) lung, each of which sounds dull to percussion. At the other extreme, air in the pleural space (pneumothorax) or a hyperinflated lung (as in emphysema) may produce a hyperresonant or more «hollow» sound, approaching what the examiner hears when percussing over a hollow viscus, such as the stomach. Additionally, the examiner can locate the approximate position of the diaphragm by a change in the quality of the percussed note, from resonant to dull, toward the bottom of the lung. A convenient aspect of the whole-chest examination is the basically symmetric nature of the two sides of the chest; a difference in the findings between the two sides suggests a localized abnormality.

When **auscultating** the lungs with a stethoscope, the examiner listens for two major features: the quality of the breath sounds and the presence of any abnormal (commonly called *adventitious*) sounds. As the patient takes a deep breath, the sound of airflow can be heard through the stethoscope. When the stethoscope is placed over normal lung tissue, sound is heard primarily during inspiration, and the quality of the sound is relatively smooth and soft. These normal breath sounds heard over lung tissue are called *vesicular breath sounds.* There is no general agreement about where these sounds originate, but the source presumably is somewhere distal to the trachea and proximal to the alveoli.

When the examiner listens over consolidated lung — that is, lung that is airless and filled with liquid or inflammatory cells — the findings are different. The sound is louder and harsher, more hollow or tubular in quality, and expiration is at least as loud and as long as inspiration. Such breath sounds are called *bronchial breath sounds,* as opposed to the normal vesicular sounds. This difference in quality of the sound is due to the ability of consolidated lung to transmit sound better than normally aerated lung. As a result, sounds generated by turbulent airflow in the

central airways (trachea and major bronchi) are transmitted to the periphery of the lung and can be heard through the stethoscope. Normally, these sounds are not heard in the lung periphery; they can be demonstrated only by listening near their site of origin — for example, over the upper part of the sternum or the suprasternal notch.

Better transmission of sound through consolidated rather than normal lung also can be demonstrated when the patient whispers or speaks. The enhanced transmission of whispered sound results in more distinctly heard syllables and is termed *whispered pectoriloquy.* Spoken words can be heard more distinctly through the stethoscope placed over the involved area, a phenomenon commonly called *bronchophony.*

Two qualifications are important in interpreting the quality of breath sounds. First, normal transmission of sound depends on patency of the airway. If a relatively large bronchus is occluded, such as by tumor, secretions, or a foreign body, airflow into that region of lung is diminished or absent, and the examiner hears decreased or absent breath sounds over the affected area. A blocked airway proximal to consolidated or airless lung also eliminates the increased transmission of sound described previously. Second, either air or fluid in the pleural space acts as a barrier to sound so that either a pneumothorax or a pleural effusion causes diminution of breath sounds.

The second major feature the examiner listens for is adventitious sounds. Unfortunately, the terminology for these adventitious sounds varies considerably among examiners; therefore, only the most commonly used terms are considered here: crackles, wheezes, and friction rubs. A fourth category, rhonchi, is used inconsistently by different examiners, thus decreasing its clinical usefulness for communicating abnormal findings.

Crackles, also called *rales,* are a series of individual clicking or popping noises heard with the stethoscope over an involved area of lung. Their quality can range from the sound produced by rubbing hairs together to that generated by opening a hook and loop fastener or crumpling a piece of cellophane. These sounds are «opening» sounds of small airways or alveoli that have been collapsed or decreased in volume during expiration because of fluid, inflammatory exudate, or poor aeration. On each subsequent inspiration, opening of these distal lung units creates the series of clicking or popping sounds heard either throughout or at the latter part of inspiration. The most common disorders producing rales are pulmonary edema, pneumonia, interstitial lung disease, and atelectasis.

Rhonchi are low-pitched respiratory sounds that can be heard during inspiration or expiration. They occur in various conditions, including chronic bronchitis. The mechanism may relate to variations in obstruction as airways distend with inhalation and narrow with exhalation.

Wheezes are high-pitched, continuous sounds that are generated by airflow through narrowed airways. Causes of such narrowing include airway smooth muscle constriction, edema, secretions, intraluminal obstruction, and collapse because of poorly supported walls.

The diameter of intrathoracic airways is less during expiration than inspiration, and wheezing generally is more pronounced or exclusively heard in expiration. However, because sufficient airflow is necessary to generate a wheeze, wheezing may no longer be heard if airway narrowing is severe. When the site of narrowing is the extrathoracic airway (e.g., in the larynx or the extrathoracic portion of the trachea), the term *stridor* is used to describe the inspiratory wheezinglike sound that results from such narrowing.

A *friction rub* is the term for the sounds generated by inflamed or roughened pleural surfaces rubbing against each other during respiration. A rub is a series of creaky or rasping sounds heard during both inspiration and expiration. The most common causes are primary inflammatory diseases of the pleura or parenchymal processes that extend out to the pleural surface, such as pneumonia and pulmonary infarction.

Although the focus here is the chest examination itself as an indicator of pulmonary disease, other **nonthoracic manifestations** of primary pulmonary disease may be detected on physical examination. Briefly discussed here are clubbing (with or without hypertrophic osteoarthropathy) and cyanosis.

Clubbing is a change in the normal configuration of the nails and the distal phalanx of the fingers or toes. Although several non-pulmonary disorders can result in clubbing (e.g., congenital heart disease with right-to-left shunting, endocarditis, chronic liver disease, inflammatory bowel disease), the most common causes clearly are pulmonary. Occasionally, clubbing is familial and of no clinical significance. Carcinoma of the lung (or mesothelioma of the pleura) is the single leading etiologic factor. Other pulmonary causes include chronic intrathoracic infection with suppuration (e.g., bronchiectasis, lung abscess, empyema) and some types of interstitial lung disease. Uncomplicated chronic obstructive lung disease is not associated with clubbing, so the presence of clubbing in this setting should suggest coexisting malignancy or suppurative disease.

Clubbing may be accompanied by *hypertrophic osteoarthropathy,* characterized by periosteal new bone formation, particularly in the long bones, and arthralgias and arthritis of any of several joints. With coexistent hypertrophic osteoarthropathy, either pulmonary or pleural tumor is the likely cause of the clubbing because hypertrophic osteoarthropathy is relatively rare with the other causes of clubbing.

Table 1.4 — Typical Chest Examination Findings in Selected Clinical Conditions

Condition	Percussion	Fremitus	Breath Sounds	Voice Transmission	Crackles
Normal	Resonant	Normal	Vesicular (at lung bases)	Normal	Absent
Consolidation or atelectasis (with patent airway)	Dull	Increased	Bronchial	Bronchophony, whispered pecto-riloquy, egophony	Present
Consolidation or atelectasis (with blocked airway)	Dull	Decreased	Decreased	Decreased	Absent
Emphysema	Hyperresonant	Decreased	Decreased	Decreased	Absent
Pneumothorax	Hyperresonant	Decreased	Decreased	Decreased	Absent
Pleural effusion	Dull	Decreased	Decreased*	Decreased*	Absent

*May be altered by collapse of underlying lung, which will increase transmission of sound.

Cyanosis, the second extrapulmonary physical finding arising from lung disease, is a bluish discoloration of the skin (particularly under the nails) and mucous membranes. Whereas oxygenated hemoglobin gives lighter skin and all mucous membranes their usual pink color, a sufficient amount of deoxygenated hemoglobin produces cyanosis. Cyanosis may be either generalized, owing to a low PO_2 or low systemic blood flow resulting in increased extraction of oxygen from the blood, or localized, owing to low blood flow and increased O_2 extraction within the localized area. In lung disease the common factor causing cyanosis is a low Po_2, and several different types of lung disease may be responsible. The total amount of hemoglobin affects the likelihood of detecting cyanosis. In the anemic patient, if the total quantity of deoxygenated hemoglobin is less than the amount needed to produce the bluish discoloration, even a very low PO_2 may not be associated with cyanosis. In the patient with polycythemia, in contrast, much less depression of PO_2 is necessary before sufficient deoxygenated hemoglobin exists to produce cyanosis.

CHEST RADIOGRAPHY

The chest radiograph, which is largely taken for granted in the practice of medicine, is used not only in evaluating patients with suspected respiratory disease but also sometimes in the routine evaluation of asymptomatic patients.

Additionally, the presence of two lungs allows each to serve as a control for the other so that unilateral abnormalities can be more easily recognized.

A few principles can aid student in viewing films.

First, the appearance of any structure on a radiograph depends on the structure's density; the denser the structure, the whiter it appears on the fi lm. At one extreme is air, which is radiolucent and appears black on

the fi lm. At the other extreme are metallic densities, which appear white. In between is a spectrum of increasing density from fat to water to bone. The viscera and muscles fall within the realm of water density tissues and cannot be distinguished in radiographic density from water or blood.

Second, in order for a line or an interface to appear between two adjacent structures on a radiograph, the two structures must differ in density. For example, within the cardiac shadow the heart muscle cannot be distinguished from the blood coursing within the chambers because both are of water density. In contrast, the borders of the heart are visible against the lungs, because the water density of the heart contrasts with the density of the lungs, which is closer to that of air. However, if the lung adjacent to a normally denser structure (e.g., heart or diaphragm) is airless, either because of collapse or consolidation, the neighboring structures are now both of the same density, and no visible interface or boundary separates them. This principle is the basis of the useful *silhouette sign.* If an expected border with an area of lung is not visualized or is not distinct, the adjacent lung is abnormal and lacks full aeration.

Chest radiographs usually are taken in two standard views — posteroanterior (PA) and lateral. Knowledge of radiographic anatomy is fundamental for interpretation of consolidation or collapse (atelectasis) and for localization of other abnormalities on the chest film. Lobar anatomy and the locations of fissures separating the lobes are shown in Figure 1.1.
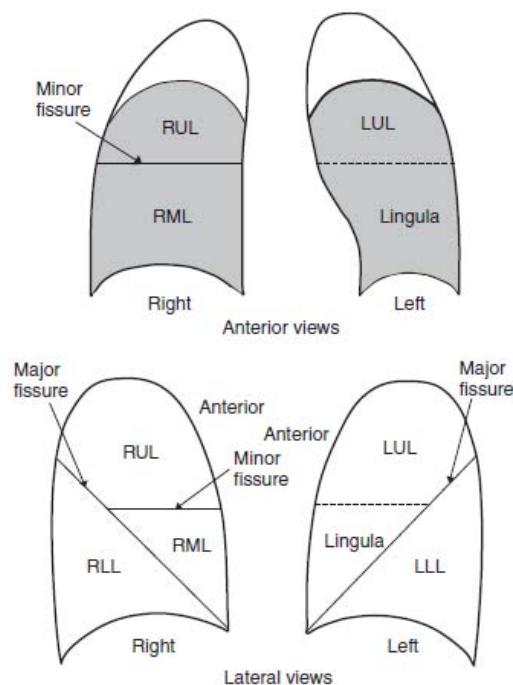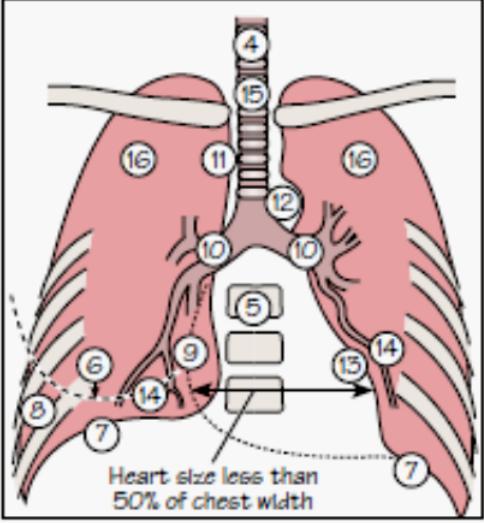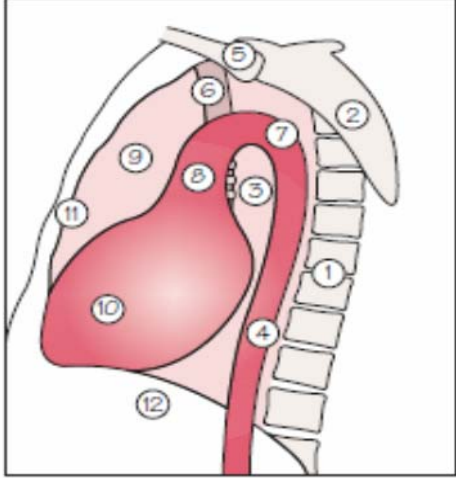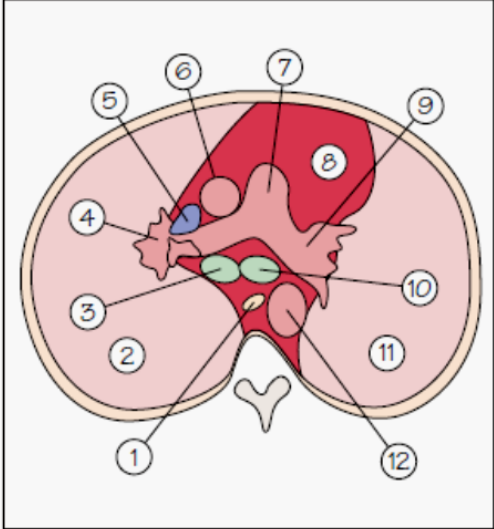

Figure 1.1. — Lobar anatomy as seen from anterior and lateral views. In anterior views, *shaded regions* represent lower lobes and are behind upper and middle lobes. Lingula is part of the left upper lobe; *dashed line* between the two does not represent a fissure. LLL — Left lower lobe; LUL — left upper lobe; RLL — right lower lobe; RML — right middle lobe; RUL — right upper lobe.

Table 1.5. — Chest Radiograph Interpretation

Evaluation of the CXR includes all the following: 1 — Date: 2 — Name 3 — AP/PA: Is it AP (anteroposterior) or PA (posteroanterior)? (Heart size cannot be measured if AP) 4 — Is it well positioned? The trachea should be midway between clavicles 5 — Penetration: The disc spaces should be just visible through the cardiac shadows (underpenetrated = plethoric lungs overpenetrated = dark lungs) 6 — Soft tissues and breast shadows (mastectomy in a female) 7 — Right diaphragm 2 cm higher than left (raised when paralysed, flat in asthma/COPD) 8 — Check ribs for fractures, metastases 9 — Right heart border = right atrium 10 — Hilium = bronchi, arteries and veins 11 — Superior vena cava 12 — Aortic arch 13 — Left heart border = left ventricle 14 — Pulmonary vessels 15 — Trachea and main bronchi 16 — Lung fields	 Heart size less than 50% of chest width
1 — Thoracic vertebral bodies 2 — Scapula 3 — Pulmonary trunk and hilium 4 — Descending aorta 5 — Head of clavicle 6 — Trachea 7 — Arch of aorta 8 — Ascending aorta 9 — Anterior space (thymus) 10 — Heart 11 — Sternum 12 — Diaphragm	
1 — Oesophagus 2 — Right lung 3 — Right main bronchus 4 — Right pulmonary artery and branches 5 — Superior vena cava 6 — Ascending aorta 7 — Pulmonary trunk 8 — Mediastinum and heart 9 — Left pulmonary artery and branches 10 — Left main bronchus 11 — Left lung 12 — Descending aorta	

COMPUTED TOMOGRAPHY

CT is particularly useful for detecting subtle differences in tissue density that cannot be distinguished by conventional radiography. In addition, the cross-sectional views obtained from the slices provide very different information from that provided by the vertical orientation of plain films.

With this technique a narrow beam of x-rays is passed through the patient and sensed by a rotating detector on the other side of the patient. The beam is partially absorbed within the patient, depending on the density of the intervening tissues. Computerized analysis of the information received by the detector allows a series of cross-sectional images to be constructed. Use of different «windows» allows different displays of the collected data, depending on the densities of the structures of interest. With the technique of helical (spiral) CT scanning, the entire chest is scanned continuously (typically during a single breathhold and using multiple detectors) as the patient's body is moved through the CT apparatus (the gantry). If radiographic contrast is injected intravenously, images of the pulmonary arterial system obtained during helical scanning (CT angiography) can be used for detection of pulmonary emboli.
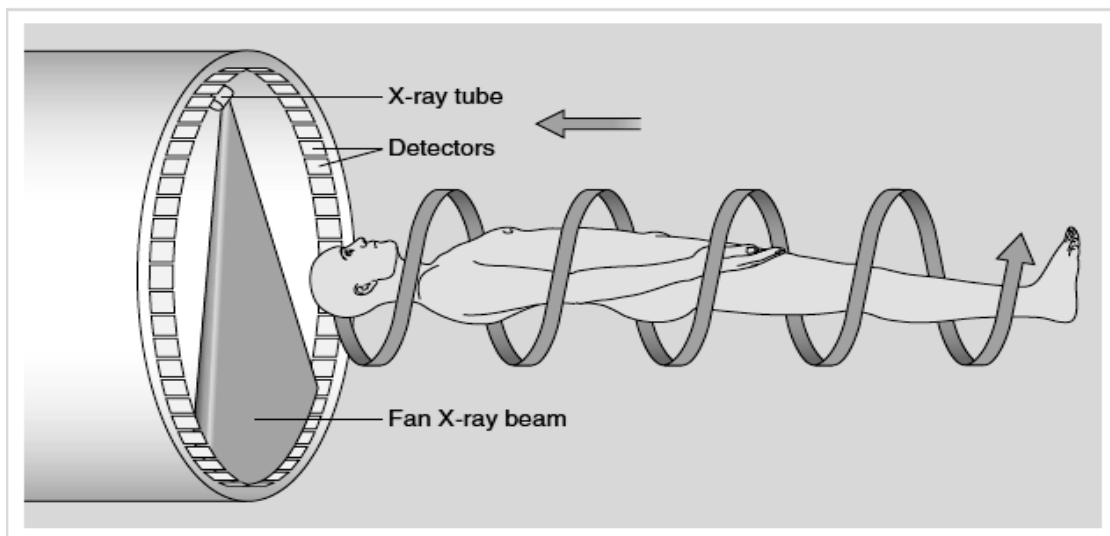
Figure 1.2. — The principle of spiral computed tomography. The patient moves into the scanner with the X-ray tube continuously rotating and the detectors acquiring information. The rapidity of data acquisition allows a complete examination of the thorax to be performed in a single breath hold

Chest CT has been used extensively in evaluating pulmonary nodules and the mediastinum. It also has been quite valuable in characterizing chest wall and pleural disease, and it now is frequently used for detecting pulmonary emboli through the technique of CT angiography. As the technology has advanced, CT has become progressively more useful in the diagnostic evaluation of various diseases affecting the pulmonary parenchyma and the airways. With high-resolution CT, the thickness of individual cross-

sectional images is reduced to 1 to 2 mm instead of the traditional 5 to 10 mm. As a result, exceptionally fine detail can be seen, allowing earlier recognition of subtle disease and better characterization of specific disease patterns.

Sophisticated software protocols now allow images obtained by CT scanning to be reconstructed and presented in any plane that best displays the abnormalities of interest. Additionally, it now is possible to produce three-dimensional images from the data acquired by CT scanning. For example, a three-dimensional view of the airways can be displayed in a manner resembling what is seen inside the airway lumen during bronchoscopy. This methodology creates an imaging tool that has been dubbed *virtual bronchoscopy.*

MAGNETIC RESONANCE IMAGING

Another radiologic technique available for evaluation of intrathoracic disease is magnetic resonance imaging (MRI). The technique depends on the way that nuclei within a stationary magnetic field change their orientation and release energy delivered to them by a radiofrequency pulse. The time required to return to the baseline energy state can be analyzed by a complex computer algorithm and a visual image created.

In the evaluation of intrathoracic disease, MRI has several important features. First, flowing blood produces a «signal void» and appears black, so blood vessels can be readily distinguished from nonvascular structures without the need to use intravenous contrast agents. Second, images can be constructed in any plane so that the information obtained can be displayed as sagittal, coronal, or transverse (cross-sectional) views. Third, differences can be seen between normal and diseased tissues that are adjacent to each other, even when they are of the same density and therefore cannot be distinguished by routine radiography or CT.

MRI scanning is expensive, so it generally is used when it can provide information not otherwise obtainable by less expensive, equally noninvasive means. Although MRI is newer than CT, it does not replace CT; rather, it often provides complementary diagnostic information. It can be a valuable tool in evaluating hilar and mediastinal disease as well as in defining intrathoracic disease that extends to the neck or the abdomen. On the other hand, it is less useful than CT in the evaluation of pulmonary parenchymal disease.

PULMONARY ANGIOGRAPHY AND COMPUTED TOMOGRAPHIC ANGIOGRAPHY

Pulmonary angiography provides useful information about pulmonary blood flow. It is a radiographic technique in which a catheter is guided from a peripheral vein, through the right atrium and ventricle, and into the main pulmonary artery or one of its branches. A radiopaque dye is injected, and

the pulmonary arterial tree is visualized on a series of rapidly exposed chest films. A clot in a pulmonary vessel appears either as an abrupt termination («cutoff») of the vessel or as a filling defect within its lumen.

The pulmonary angiogram has other uses, including investigation of congenital vascular anomalies and invasion of a vessel by tumor. However, use of the angiogram in these situations is quite infrequent.

More recently, CT angiography, in which the pulmonary arterial system is visualized by helical CT scanning following injection of radiographic contrast into a peripheral vein, has been increasingly used in place of both perfusion lung scanning and traditional pulmonary angiography. Its use is attractive because it is less invasive than traditional pulmonary angiography. Although CT angiography is not as sensitive as traditional angiography for detecting emboli in relatively small pulmonary arteries, ongoing improvements in CT scanner technology have provided better identification of clots in progressively smaller pulmonary arteries.

ULTRASONOGRAPHY

The ability of different types of tissue to transmit sound and of tissue interfaces to reflect sound has made ultrasonography useful for evaluating a variety of body structures. A piezoelectric crystal generates sound waves, and the reflected echoes are detected and recorded by the same crystal. Images are displayed on a screen and can be captured for a permanent record.

The heart is the intrathoracic structure most frequently studied by ultrasonography, but the technique is also useful in evaluating pleural disease. In particular, ultrasonography is capable of detecting small amounts of pleural fluid and is often used to guide placement of a needle for sampling a small amount of this fluid. It can detect walled-off compartments (loculations) within pleural effusions and distinguish fluid from pleural thickening.

Ultrasonography is capable of localizing the diaphragm and detecting disease immediately below the diaphragm, such as a subphrenic abscess. Ultrasonography is not useful for defining structures or lesions within the pulmonary parenchyma because the ultrasound beam penetrates air poorly.

BRONCHOSCOPY

Direct visualization of the airways is possible by bronchoscopy, originally performed with a hollow, rigid metal tube and now much more commonly with a thin flexible instrument. The flexible instrument transmits images either via flexible fiberoptic bundles (traditional fiberoptic bronchoscope) or more recently, and now much more commonly, via a digital chip at the tip of the bronchoscope that displays the images on a monitor screen. Because the bronchoscope is flexible, the bronchoscopist can bend the tip with a control lever and maneuver into airways at least down to the subsegmental level.
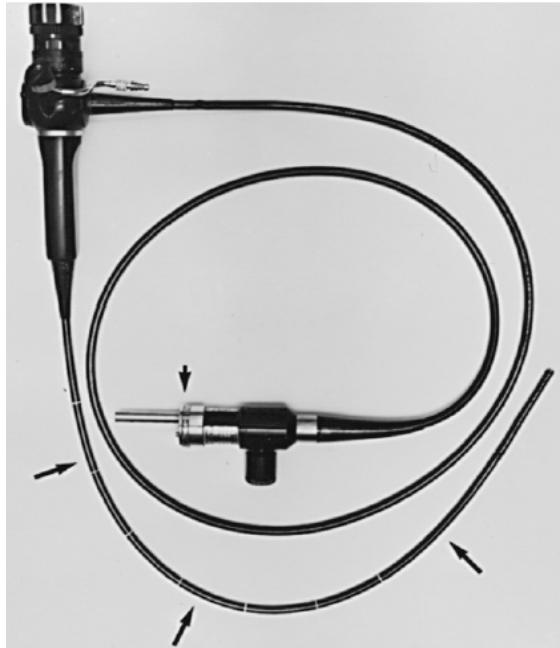
Figure 1.3. — Flexible bronchoscope. *Long arrows* **point to flexible part passed into patient's airways.** *Short arrow* **points to portion of bronchoscope connected to light source. Controls for clinician performing the procedure are shown at upper left.**

The bronchoscopist can obtain an excellent view of the airways and collect a variety of samples for cytologic, pathologic, and microbiologic examination. Sterile saline can be injected through a small, hollow channel in the bronchoscope and suctioned back into a collection chamber. This technique, called *bronchial washing,* samples cells and, if present, microorganisms from the lower respiratory tract. When the bronchoscope is passed as far as possible and wedged into an airway before saline is injected, the washings are able to sample the contents of the alveolar spaces; this technique is called *bronchoalveolar lavage* (BAL).

A long flexible wire instrument with a small brush at the tip can be passed through the hollow channel of the bronchoscope. The surface of a lesion within a bronchus can be brushed and the cells collected or smeared onto a slide for cytologic examination. Brushes are frequently passed into diseased areas of the lung parenchyma, and the material collected by the bristles is subjected to cytologic and microbiologic analysis.

A needle at the end of a long catheter passed through the bronchoscope can puncture an airway wall and sample cells from lymph nodes or lesions adjacent to the airway. This technique, called *transbronchial needle aspiration,* can be used to obtain malignant cells from mediastinal lymph nodes in the staging of known or suspected lung cancer. Using an ultrasound probe within the airway during bronchoscopy *(endobronchial ultrasound)* can help the bronchoscopist localize mediastinal lymphnodes that are external to the airway and therefore greatly assist with accurate placement of a needle into the node for transbronchial needle aspiration.

With a small biopsy forceps passed through the bronchoscope, the clinician can extract a biopsy specimen from a lesion visualized on the bronchial wall *(endobronchial biopsy).* When a fluoroscope is used to aid in passage of the forceps, the lung parenchyma is quite accessible after the forceps puncture a small bronchus and move out into the distal parenchyma. This procedure, known as a *transbronchial biopsy,* yields pieces of tissue that are small but have a sizable number of alveoli.

There are many indications for bronchoscopy, usually with a flexible instrument, although the rigid instrument is used under some circumstances. When appropriate, the flexible instrument is preferred because the procedure can be performed using only mild sedation and the patient need not be hospitalized. In contrast, rigid bronchoscopy is performed only under general anesthesia. Some indications for bronchoscopy include (1) evaluation of a suspected endobronchial malignancy; (2) sampling of an area of parenchymal disease by BAL, brushings, or biopsy; (3) evaluation of hemoptysis; and (4) removal of a foreign body (with special instruments that can be passed through the bronchoscope and are capable of retrieving objects).

EVALUATION ON A MICROSCOPIC LEVEL

Microscopy often provides the definitive diagnosis of pulmonary disease suggested by the history, physical examination, or chest radiograph. Several types of disorders are particularly amenable to diagnosis by microscopy: lung tumors (by either histology or cytology), pulmonary infection (by microscopic identification of a specific organism), and a variety of miscellaneous pulmonary diseases, particularly those affecting the interstitium of the lung (by histology). Frequently, when a diagnosis is uncertain, the same techniques are used to obtain samples that are processed both for histologic (or cytologic) examination and for identification of microorganisms.

OBTAINING SPECIMENS

The three main types of specimens the physician uses for microscopic analysis in diagnosing the patient with lung disease are (1) tracheobronchial secretions, (2) tissue from the lung parenchyma, and (3) fluid or tissue from the pleura. A number of methods are available for obtaining each of these types of specimens, and knowledge of the yield and the complications determines the most appropriate method.

The easiest way to obtain a specimen of tracheobronchial secretions is to collect sputum that is expectorated spontaneously by the patient. The sample can be used for identifying inflammatory or malignant cells and for staining (and culturing) microorganisms.

Collecting sputum sounds simple, but it presents several potential problems. First, the patient may not have any spontaneous cough and

sputum production. If this is the case, sputum frequently can be induced by having the patient inhale an irritating aerosol, such as hypertonic saline. Second, what is thought to be sputum originating from the tracheobronchial tree frequently is either nasal secretions or «spit» expectorated from the mouth or the back of the throat. Finally, as a result of passage through the mouth, even a good, deep sputum specimen is contaminated by the multiplicity of microorganisms that reside in the mouth. Because of this contamination, care is required in interpreting the results of sputum culture, particularly with regard to the normal flora of the upper respiratory tract. Despite these limitations, sputum remains a valuable resource when looking for malignancy and infectious processes such as bacterial pneumonia and tuberculosis.

Tracheobronchial secretions also can be obtained by bronchoscopy.

Bronchoscopy, generally with a flexible instrument, is a suitable way to obtain tracheobronchial secretions. Bronchoscopy has distinct advantages in collecting material for cytologic analysis because specimens can be collected from a localized area directly visualized with the bronchoscope. Specially designed systems with a protected brush can decrease contamination, and quantitating the bacteria recovered can be helpful in distinguishing upper airway contamination from true lower respiratory infection.

BAL has become an increasingly popular method for obtaining specimens from the lower respiratory tract. The fluid obtained by BAL has been used quite effectively for detecting *P. jiroveci,* particularly in patients with AIDS. In some interstitial lung diseases analysis of the cellular and biochemical components of BAL may provide information that is useful diagnostically and for research about basic disease mechanisms.

As is true of tracheobronchial secretions, tissue specimens for microscopic examination can be collected in numerous ways. A brush or a biopsy forceps can be passed through a bronchoscope. The brush is often used to scrape cells from the surface of an airway lesion, but it also can be passed more distally into the lung parenchyma to obtain specimens directly from a diseased area. The biopsy forceps is used in a similar fashion to sample tissue either from a lesion in the airway (endobronchial biopsy) or from an area of disease in the parenchyma (transbronchial biopsy, so named because the forceps must puncture a small bronchus to sample the parenchyma). In the case of bronchial brushing, the specimen that adheres to the brush is smeared onto a slide for staining and microscopic examination. For both endobronchial and transbronchial biopsies, the tissue obtained can be fixed and sectioned, and slides can be made for subsequent microscopic examination.

A lesion or diseased area in the lung parenchyma can be reached with a needle through the chest wall. Depending on the type of needle used, a small sample may be aspirated or taken by biopsy. Bleeding and pneumothorax are potential complications, just as they are for a transbronchial biopsy with a bronchoscope.

Lung tissue is frequently obtained by a surgical procedure involving an approach through the chest wall. Traditionally, a surgeon made an incision in the chest wall, allowing direct visualization of the lung surface and removal of a small piece of lung tissue. This type of open lung biopsy has largely been supplanted by a less invasive procedure called *thoracoscopy* (or *video-assisted thoracic surgery*). Video-assisted thoracic surgery involves placement of a thoracoscope and biopsy instruments through small incisions in the chest wall; a high-quality image obtained through the thoracoscope can be displayed on a monitor screen. The surgeon uses the video image as a guide for manipulating the instruments to obtain a biopsy sample of peripheral lung tissue or to remove a peripheral lung nodule.

Finally, fluid in the pleural space is frequently sampled in the evaluation of a patient with a pleural effusion. A small needle is inserted through the chest wall and into the pleural space, and fluid is withdrawn. The fluid can be examined for malignant cells and microorganisms. Chemical analysis of the fluid often provides additional useful diagnostic information. A biopsy specimen of the parietal pleural surface (the tissue layer lining the pleural space) also may be obtained either blindly, with a special needle passed through the chest wall, or under direct visualization using a thoracoscope. The tissue can be used for microscopic examination and microbiologic studies.

PROCESSING SPECIMENS
Once the specimens are obtained, the techniques of processing and the types of examination performed are common to those used for many types of tissue and fluid specimens.

Diagnosis of pulmonary infections depends on smears and cultures of the material obtained, such as sputum, other samples of tracheobronchial secretions, or pleural fluid. The standard Gram stain technique often allows initial identification of organisms, and inspection may reveal inflammatory cells (particularly polymorphonuclear leukocytes) and upper airway (squamous epithelial) cells, the latter indicating contamination of sputum by upper airway secretions. Final culture results provide definitive identification of an organism, but the results must always be interpreted with the knowledge that the specimen may be contaminated and that what is grown is not necessarily causally related to the clinical problem.

Identification of mycobacteria, the causative agent for tuberculosis, requires special staining and culturing techniques. Frequently used staining methods are the Ziehl-Neelsen stain. A more sensitive and faster way to detect mycobacteria involves use of a fluorescent dye such as auraminerhodamine. Mycobacteria take up the dye and fluoresce and can be detected relatively easily even when present in small numbers. Because mycobacteria grow slowly, they may require 6 to 8 weeks for growth and identification on culture media.

Organisms other than the common bacterial pathogens and mycobacteria often require other specialized staining and culture techniques. Fungi may be diagnosed by special stains, such as methenamine silver or periodic acid — Schiff stains, applied to tissue specimens. Fungi also can be cultured on special media favorable to their growth. *Pneumocystis jiroveci,* a pathogen that is most common in patients with impaired defense mechanisms, is stained in tissue and tracheobronchial secretions by methenamine silver, toluidine blue, or Giemsa stain. An immunofluorescent stain using monoclonal antibodies against *Pneumocystis* is particularly sensitive for detecting the organism in sputum and BAL fluid. *Legionella pneumophila,* the causative agent of legionnaires' disease, can be diagnosed by silver impregnation or immunofluorescence staining. The organism also can be grown, with difficulty, on some special media.

Cytologic examination for malignant cells is available for expectorated sputum, specimens obtained by needle aspiration, bronchial washings or brushings obtained with a bronchoscope, and pleural fluid. A specimen can be smeared directly onto a slide (as with a bronchial brushing), subjected to concentration (bronchial washings, pleural fluid), or digested (sputum) prior to being smeared on the slide. The slide then is stained by the Papanicolaou technique, and the cells are examined for findings suggestive or diagnostic of malignancy. Pathologic examination of tissue sections obtained by biopsy is most useful for diagnosis of malignancy or infection as well as for a variety of other processes affecting the lungs and the pleura. In many circumstances, examination of tissue obtained by biopsy is the gold standard for diagnosis, although even biopsy results can show falsenegative findings or yield misleading information.

Tissue obtained by biopsy is routinely stained with hematoxylin and eosin for histologic examination. A wide assortment of other stains is available that more or less specifically stain collagen, elastin, and a variety of microorganisms.

There has been great interest in applying state-of-the-art molecular biologic techniques to respiratory specimens for diagnosis of certain types of respiratory tract infection. For example, the polymerase chain reaction uses specific synthetic oligonucleotide «primer» sequences and DNA polymerase to amplify DNA that is unique to a specific organism. If the particular target DNA sequence is present, even if only from a single organism, sequential amplification allows production of millions of copies, which can be detected by gel electrophoresis. This technique can be applied to samples such as sputum and BAL, providing an exquisitely sensitive test for identifying organisms such as mycobacteria, *P. jiroveci,* and cytomegalovirus.

PULMONARY FUNCTION TESTS

Pulmonary function testing provides an objective method for assessing functional changes in a patient with known or suspected lung dis-

ease. With the results of tests that are widely available, the physician can answer several questions: (1) Does the patient have significant lung disease sufficient to cause respiratory impairment and to account for his or her symptoms? (2) What functional pattern of lung disease does the patient have — restrictive or obstructive disease?

Three main categories of information can be obtained with routine pulmonary function testing:

1. Lung volumes, which provide a measurement of the size of the various compartments within the lung

2. Flow rates, which measure maximal flow within the airways

3. Diffusing capacity, which indicates how readily gas transfer occurs from the alveolus to pulmonary capillary blood.

Lung Volumes. Although the lung can be subdivided into compartments in different ways, four volumes are particularly important:

1. Total lung capacity (TLC): Total volume of gas within the lungs after a maximal inspiration.

2. Residual volume (RV): Volume of gas remaining within the lungs after a maximal expiration.

3. Vital capacity (VC): Volume of gas expired when going from TLC to RV.

4. Functional residual capacity (FRC): Volume of gas within the lungs at the resting state, that is, at the end of expiration during the normal tidal breathing pattern.

Lung volumes are determined by spirometry and either gas dilution or body plethysmography.

VC can be measured by having the patient exhale into a spirometer from TLC down to RV. By definition, the volume expired in this manner is the VC. However, because RV, FRC, and TLC all include the amount of gas left within the lungs even after a maximal expiration, these volumes cannot be determined simply by having the patient breathe into a spirometer. To quantitate these volumes, a variety of methods can measure one of these three volumes, and the other two volumes then can be calculated or derived from the spirometric tracing.
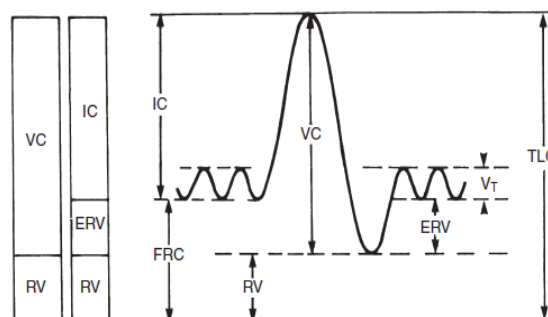

Figure 1.4. — Subcompartments of lung (lung volumes). On the *right,* lung volumes are labeled on spirographic tracing. On the *left,* block diagrams show two ways that total lung capacity can be subdivided. ERV — Expiratory reserve volume; FRC — functional residual capacity; IC — inspiratory capacity; RV — residual volume; TLC — total lung capacity; VC — vital capacity; VT — tidal volume

1. Dilution tests: A known volume of an inert gas (usually helium) at a known concentration is inhaled into the lungs. This gas is diluted by the volume of gas already present within the lungs, and the concentration of expired gas (relative to inspired) therefore reflects the initial volume of gas in the lungs.

2. Body plethysmography: The patient, sitting inside an airtight box, performs a maneuver that causes expansion and compression of gas within the thorax. By quantitating volume and pressure changes and by applying Boyle's law, the volume of gas in the thorax can be calculated.

Flow Rates. Measurement of flow rates on routine pulmonary function testing involves assessing airflow during maximal forced expiration, that is, with the patient blowing out as hard and as fast as possible from TLC down to RV. The volume expired during the first second of such a forced expiratory maneuver is called the *forced expiratory volume in 1 second* (FEV1). When pulmonary function tests are interpreted, FEV1 is routinely compared with VC, or with VC specifically measured during the forced expiratory maneuver called the *forced vital capacity* (FVC). In interpreting flow rates, the ratio between these two measurements (FEV1/VC or FEV1/FVC) is the most important number used to determine the presence of obstruction to airflow. Another parameter often calculated from the forced expiratory maneuver is the maximal midexpiratory flow rate (MMFR), which is the rate of airflow during the middle one-half of the expiration (between 25 % and 75 % of the volume expired during the FVC). MMFR is frequently called the forced expiratory flow (FEF) between 25 % and 75 % of vital capacity (FEF 25%–75 %). The MMFR or FEF 25%–75 % is a relatively sensitive index of airflow obstruction and may be abnormal when the FEV1/FVC ratio is still preserved.
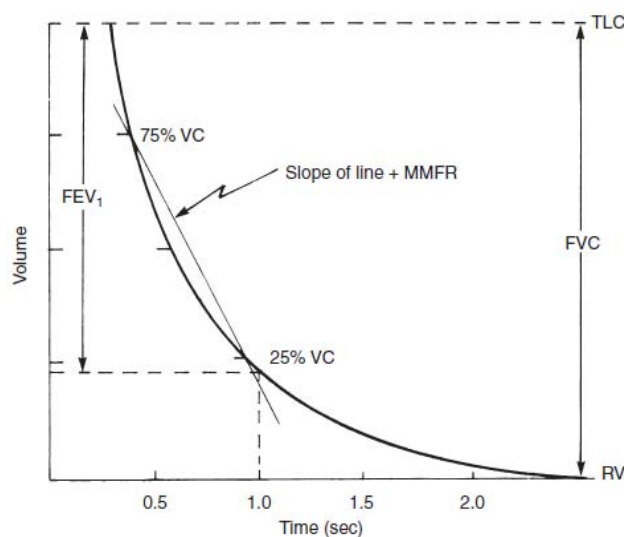
Figure 1.5. — Forced expiratory spirogram. Volume is plotted against time while patient breathes out as hard and fast as possible from total lung capacity (TLC) to residual volume (RV). FEV1 — Forced expiratory volume in 1 second; FVC — forced vital capacity; MMFR — maximal midex piratory flow rate (also called forced expiratory flow from 25–75 % [FEF 25%-75%]); VC — vital capacity

Table 1.6. — Definition of Common Spirometric Values

Reported value	Description	Interpretation
VC	Vital capacity Volume of air displaced by maximal exhalation or maximal inhalation maneuver	Typically preserved in obstruction, but reduced in restriction
FVC	Forced vital capacity Volume forcefully exhaled from maximal inhalation (TLC) to maximal exhalation (RV), the FEVC maneuver	Pattern similar to VC, although more likely to be reduced in obstruction than VC. Used to grade severity of restriction.
FEV_1	Forced expiratory volume in one second Volume exhaled in 1st second of FEVC maneuver	Reduction typical of medium to large airways obstruction. Used to grade severity of obstruction.
FEV_1/FVC	Ratio of FEV1 to FVC	Reductions indicative of airway obstruction.
FEF_{25-75}	Forced expiratory flow (25–75 %) Mean expiratory flow rate in the middle half of FEV maneuver	Sensitive but nonspecific indicator of small airways obstruction. Poorly reproducible, varies with effort and time of expiration.
PEF	Peak expiratory flow Maximal sustained airflow achieved during the FEVC maneuver	Worsening may correlate with asthma exacerbations. Sometimes helpful in assessing subject effort

A significant amount of work was performed in the past to develop tests that detect early obstruction to airflow, particularly when it is due to small or peripheral airways obstruction. Such tests include maximal expiratory flow-volume loops, analysis of closing volume, and frequency-dependent dynamic compliance. The flow-volume loop is a graphic record of maximal inspiratory and maximal expiratory maneuvers. However, rather than the graph of volume versus time that is given with usual spirometric testing, the flow-volume loop has a plot of flow (on the Y-axis) versus volume (on the X-axis).
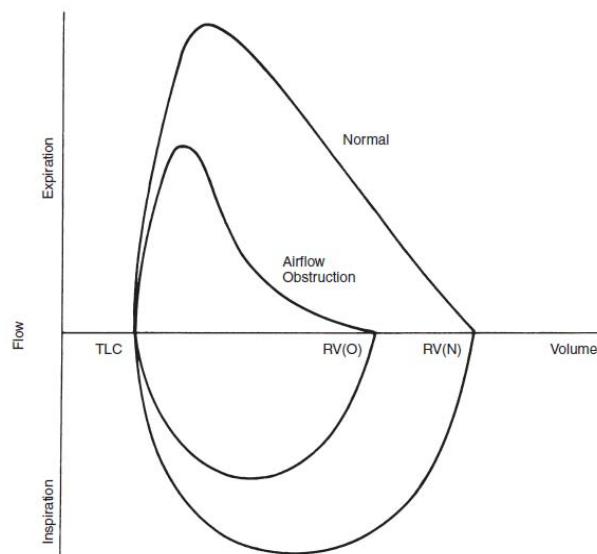
Figure 1.6. — Flow-volume loops in normal individual and patient with airflow obstruction.
Expiratory «coving» is apparent on tracing of patient with airflow obstruction.
RV(N) — Residual volume in normal individual; RV(O) — residual volume in patient
with obstructive disease; TLC — total lung capacity

Diffusing Capacity. The diffusing capacity is a measurement of the rate of transfer of gas from the alveolus to hemoglobin within a capillary, measured in relation to the driving pressure of the gas across the alveolar-capillary membrane. Small concentrations of carbon monoxide are generally used for this purpose. Carbon monoxide combines readily with hemoglobin, and the rate of transfer of gas from the alveolus to the capillary depends on movement through the alveolar-capillary membrane and the amount of hemoglobin available for binding the carbon monoxide.

Although the diffusing capacity may be influenced to some extent by the thickness of the alveolar-capillary membrane, it is most dependent on the number of functioning alveolar-capillary units, that is, the surface area available for gas exchange, and the volume of blood (hemoglobin) in the pulmonary capillaries available to bind carbon monoxide. In practice, the diffusing capacity is commonly decreased in three categories of disease in which surface area for gas exchange is lost, pulmonary capillary blood volume is decreased, or both: (1) emphysema, (2) interstitial lung disease, and (3) pulmonary vascular disease. In disorders that affect only the airways and not pulmonary parenchymal tissue (e.g., asthma, chronic bronchitis), diffusing capacity is generally preserved. On the other hand, the diffusing capacity may be elevated in cases of recent intrapulmonary hemorrhage as a result of uptake of carbon monoxide by hemoglobin in the erythrocytes within the alveolar spaces.

Patterns of Pulmonary Function Impairment

In the analysis of pulmonary function tests, abnormalities usually are categorized as one of two patterns (or a combination of the two): (1) an *obstructive* pattern, characterized mainly by obstruction to airflow, and (2) a *restrictive* pattern, with evidence of decreased lung volumes but no airflow obstruction.
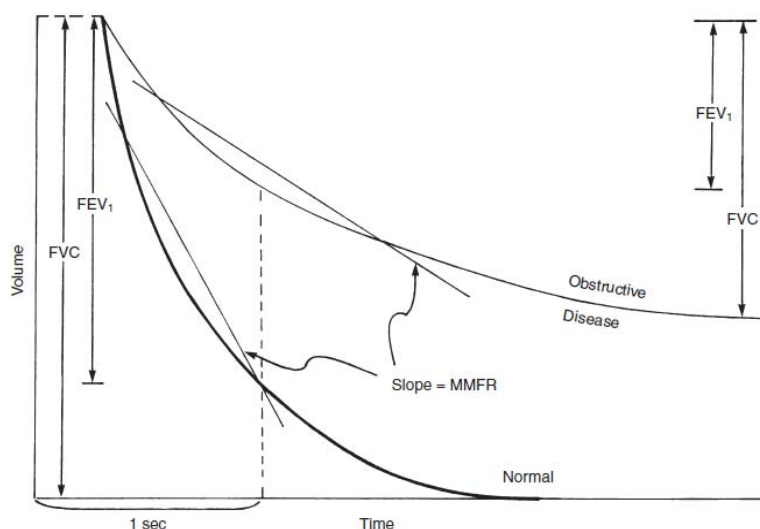
Figure 1.7. — Forced expiratory spirograms in normal individual and patient with airflow obstruction. Note prolonged expiration and changes in forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1) in patient with obstructive disease. MMFR — Maximal midexpiratory flow rate

An obstructive pattern, as seen in patients with asthma, chronic obstructive pulmonary disease, and emphysema, consists of a decrease in rates of expiratory airflow and usually manifests as a decrease in MMFR and FEV1/FVC ratio (Figure 1.7). There is generally a high RV and an increased RV/TLC ratio, indicating air trapping owing to closure of airways during forced expiration (Figure 1.8).

Hyperinflation, reflected by an increased TLC, is often found, particularly in patients with either asthma or emphysema. Diffusing capacity tends to be decreased in patients who have loss of alveolar-capillary bed (as seen in emphysema) but not in those without loss of available surface area for gas exchange (as in COPD and asthma).
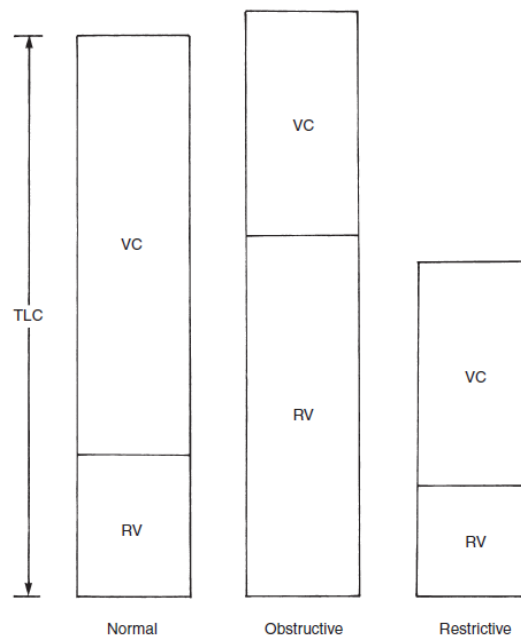
Figure 1.8. — Diagram of lung volumes (total lung capacity [TLC] and subcompartments vital capacity [VC] and residual volume [RV]) in normal individual and patients with obstructive and restrictive disease

The hallmark of restrictive disease is a reduction in lung volumes, whereas expiratory airflow is normal (see Figures 3–18). Therefore, TLC, RV, VC, and FRC all tend to be reduced, whereas MMFR and FEV1/FVC are preserved. In some patients with significant loss of volume resulting from restrictive disease, MMFR is decreased because less volume is available to generate a high flow rate. A wide variety of parenchymal, pleural, neuromuscular, and chest wall diseases can demonstrate a restrictive pattern.

ARTERIAL BLOOD GASES

Despite the extensive information provided by pulmonary function tests, they do not show the net effect of lung disease on gas exchange, which is easily assessed by studies performed on arterial blood. Arterial blood can be conveniently sampled by needle puncture of a radial artery

or, less commonly and with more potential risk, of a brachial or femoral artery. The blood is collected into a heparinized syringe (to prevent clotting), and care is taken to expel air bubbles from the syringe and to analyze the sample quickly (or to keep it on ice until analyzed). Three measurements are routinely obtained: arterial Po_2, Pco_2, and pH.

Arterial Po_2 normally is between 80 and 100 mm Hg, but the expected value depends significantly on the patient's age and the simultaneous level of Pco_2 (reflecting alveolar ventilation, an important determinant of alveolar and, secondarily, arterial Po_2). From the arterial blood gases, the alveolar-arterial oxygen gradient ($AaDo_2$) can be calculated. Normally, the difference between alveolar and arterial Po_2 is less than 10 to 15 mm Hg, but again this value depends on the patient's age. The oxygen content of the blood does not begin to fall significantly until the arterial Po_2 drops below approximately 60 mm Hg. Therefore, an abnormally low Po_2 generally does not affect O_2 transport to the tissues until it drops below this level and the saturation falls.

The range of normal arterial Pco_2 is approximately 36 to 44 mm Hg, with a corresponding pH between 7.44 and 7.36. Respiratory and metabolic factors interact closely in determining these numbers and a patient's acid-base status. Pco_2 and pH should be interpreted simultaneously because both pieces of information are necessary to distinguish respiratory from metabolic abnormalities.

In practice, the clinician considers three fundamental questions in defining all acid-base disturbances: (1) Is there an acidosis or alkalosis? (2) Is the primary disorder of respiratory or metabolic origin? (3) Is there evidence for respiratory or metabolic compensation?

Pulse Oximetry

Although direct measurement of arterial blood gases provides the best method for assessing gas exchange, it requires collection of blood by arterial puncture. Sampling of arterial blood is uncomfortable for patients, and a small but finite risk is associated with arterial puncture. As a result, pulse oximetry, a noninvasive method for assessing arterial oxygenation, has come into widespread use, particularly for hospitalized patients. The pulse oximeter is clipped onto a patient's finger, and specific wavelengths of light are passed through the finger. Oxygenated and deoxygenated hemoglobin have different patterns of light absorption, and measurement of the pulsatile absorption of light by arteriolar blood passing through the finger allows quantitation of the two forms of hemoglobin. However, certain limitations are inherent to pulse oximetry: (1) the oximeter measures O_2 saturation rather than PO_2, (2) no information is provided about CO_2 elimination and acid-base status, and (3) the results typically are inaccurate in the presence of an abnormal hemoglobin such as carboxyhemoglobin, as seen in carbon monoxide poisoning.

2. BRONCHITIS

ACUTE BRONCHITIS is inflammation of the upper airways, commonly following a URI. The cause is usually a viral infection, though it is sometimes a bacterial infection; the pathogen is rarely identified. The most common symptom is cough, with or without fever, and possibly sputum production.

Acute bronchitis is frequently a component of a URI caused by rhinovirus, parainfluenza, influenza A or B, respiratory syncytial virus, coronavirus, or human metapneumovirus. Less common causes may be Mycoplasma pneumoniae, Bordetella pertussis, and Chlamydia pneumoniae. Patients at risk include those who smoke and those with COPD or other diseases that impair bronchial clearance mechanisms, such as cystic fibrosis or conditions leading to bronchiectasis.

Symptoms and Signs

Symptoms are a nonproductive or minimally productive cough accompanied or preceded by URI symptoms. Subjective dyspnea results from chest pain or tightness with breathing, not from hypoxia, except in patients with underlying lung disease. Signs are often absent but may include scattered rhonchi and wheezing. Sputum may be clear, purulent, or, occasionally, bloody. Sputum characteristics do not correspond with a particular etiology (ie, viral vs bacterial). Mild fever may be present, but high or prolonged fever is unusual and suggests influenza or pneumonia.

On resolution, cough is the last symptom to subside and often takes several weeks or even longer to do so.

Diagnosis:

• Clinical evaluation.
• Sometimes chest x-ray.

Diagnosis is based on clinical presentation. Chest x-ray is necessary only if findings suggest pneumonia (eg, abnormal vital signs, crackles, signs of consolidation, hypoxemia). Sputum Gram stain and culture usually have no role.

Cough resolves within 2 wk in 75 % of patients. Patients with persistent cough should undergo a chest x-ray. Evaluation for pertussis, with a culture from nasopharyngeal secretions, and noninfectious etiologies, such as postnasal drip, allergic rhinitis, and cough-variant asthma, may be needed.

Treatment

• Symptom relief (acetaminophen, hydration, possibly antitussives).
• Inhaled β-agonist or anticholinergic for wheezing.
• Sometimes oral antibiotics for patients with purulent sputum.

Acute bronchitis in otherwise healthy patients is a major reason that antibiotics are overused. Nearly all patients require only symptomatic treat-

ment, such as acetaminophen and hydration. Antitussives should be used only if the cough is interfering with sleep. Patients with wheezing may benefit from an inhaled β_2-agonist (eg, albuterol) or an anticholinergic (eg, ipratropium) for ≤ 7 days. If cough persists for > 2 wk because of airway irritation, some patients benefit from a few days of inhaled corticosteroids. Oral antibiotics are typically not used except in patients with purulent sputum.

Drugs include amoxicillin 500 mg po tid for 7 days, doxycycline 100 mg po bid for 7 days, azithromycin 500 mg po once/day for 4 days, or trimethoprim/sulfamethoxazole 160/800 mg po bid for 7 days.

CHRONIC BRONCHITIS is defined as a cough that occurs every day with sputum production that lasts for at least 3 months, two years in a row.

Risk factors for chronic bronchitis:

• tobacco smoking and second-hand tobacco smoke exposure;

• prolonged exposure to adverse environmental, occupational and domestic factors (dust, fumes in the air, sniffing acid and alkali, sulfur dioxide, etc.);

• frequent viral infections;

• deficiency of α_1-antitrypsin;

• chronic tonsillitis, rhinitis, sinusitis, pharyngitis, carious teethes, violation of nasal breathing of any type (eg, nasal polyposis, and others);

• alcohol abuse (alcohol, ingested, stands mucosal bronchial tubes and has a damaging effect on it);

• chronic renal failure (highlight mucous cladding products of nitrogen metabolism bronchi cause its damage).

More than half the cases of exacerbation of chronic bronchitis due to mergertion of secondary bacterial infection, which determines the further course and progressiontion of the disease.

Many of the bronchi develop chronic inflammation with swelling and excess mucus production. The inflammation causes a change in the lining cells of the airways to varying degrees. Many cells that line the airway lose the function of their cilia (hair-like appendages that are capable of beating rapidly), and eventually the ciliated cells are lost. Cilia perform the function of moving particles and fluid (usually mucus) over the lining surface in such structures as the trachea, bronchial tubes, and nasal cavities to keep these hollow structures clear of particles and fluids. These ciliated cells that help in clearance of secretions are often replaced by so-called goblet cells. This group of cells secretes mucus into the airway. The warm moist environment of the airway along with the nutrients in the mucus is an excellent medium for growing bacteria. The mucus often becomes infected and discolored from the bacterial overgrowth and the body's inflammatory response to it. The inflammation, swelling, and mucus frequently and significantly inhibit the airflow to and from the lung alveoli by narrowing and partially obstructing the bronchi and bronchioles.

The muscles that surround the some of the airways can be stimulated by this airway irritation. This muscular spasm also known as bronchospasm can

result in further airway narrowing. With long standing inflammation, as can be seen in chronic bronchitis, this muscular spasm and inflammation results in a fixed, nonreversible narrowing of the airway and the condition is termed chronic obstructive pulmonary disease (COPD). Chronic coughing develops as the body attempts to open and clear the bronchial airways of particles and mucus or as an overreaction to ongoing inflammation. Chronic bronchitis can be a progressive disease; symptoms (listed below) increase over time.

Although people of any age can develop chronic bronchitis, the majority of people diagnosed with the disease are 45 years of age or older.

Symptoms and Signs

Diagnostic criteria of chronic bronchitis are the following:
• Presence of risk factors;
• long, intermittent or persistent cough (at least 3 months in the first-doo for the past 2 years);
• No other bronchopulmonary diseases;
• auscultatory signs of bronchial tree (hard breathing set, dry rales).

In the phase of remission patients may be concerned with a constant cough sputum, but these symptoms are not significantly disturb the quality of life. The reason for the visit to a doctor is usually an exacerbation of chronic bronchitis, characterized by:
• increased cough;
• increasing the number of detachable sputum;
• decompensation concomitant somatic diseases (increase heart failure in patients with coronary artery disease, increased blood glucose levels in diabetics and others);
• fever.

UAC without significant changes. In marked exacerbation of purulent bronchitis possible small neutrophilic leukocytosis and a moderate increase in ESR.

Sputum may be mucous or purulent. A microscopic examination of purulent sputum revealed a large number of neutrophils, cells tion bronchial epithelium, macrophages, bacterial cells. Bacteriological study of mock company identifies different types of pathogens.

Chest X-ray is performed for differential diagnosis and exception all other bronchopulmonary diseases.

Treatment

• Empiric antibiotic therapy is not recommended
• Antibiotic indications include severe acute exacerbations with increased dyspnea, as well as change in sputum viscosity, purulence, and/or volume.
• Symptomatic treatment includes the use of cough suppressants (dextromethorphan or codeine), mucolytics, and bronchodilators (albuterol).
• Patient should avoid environmental irritants, especially cigarette smoke.

3. CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Chronic Obstructive Pulmonary Disease (COPD) is a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases.

COPD remains a major public health problem. In 1998, in an effort to bring more attention to the management and prevention of COPD, a committed group of scientists formed the Global Initiative for Chronic Obstructive Lung Disease (GOLD). In 2001, the GOLD program released a consensus report, Global Strategy for the Diagnosis, Management, and prevention of COPD, this document was revised in 2006, 2011 and 2013.

Risk Factors for COPD

• Worldwide, cigarette smoking is the most commonly encountered risk factor for COPD.

• The genetic risk factor that is best documented is a severe hereditary deficiency of α_1-antitrypsin. It provides a model for how other genetic risk factors are thought to contribute to COPD.

• Of the many inhalational exposures that may be encountered over a lifetime, only tobacco smoke and occupational dusts and chemicals (vapors, irritants, and fumes) are known to cause COPD on their own. More data are needed to explore the causative role of other risk factors.

• Indoor air pollution, especially from burning biomass fuels in confined spaces, is associated with increased risk for COPD in developing countries, especially among women.

PATHOLOGY

Pathological changes characteristic of COPD are found in the proximal airways, peripheral airways, lung parenchyma, and pulmonary vasculature. These changes include chronic inflammation, and structural changes resulting from repeated injury and repair.

Inhaled cigarette smoke and other noxious particles cause lung inflammation, a normal response which appears to be amplified in patients who develop COPD.

There is a characteristic pattern of inflammation in the lungs of COPD patients, with increased numbers of neutrophils (in the airway lumen), macrophages (airway lumen, airway wall, and parenchyma), and CD8+ lymphocytes (airway wall and parenchyma). The pattern is different from that seen in asthma.

Lung inflammation is further amplified by oxidative stress and an excess of proteases in the lung. Protease-mediated destruction of elastin, a

major connective tissue component in lung parenchyma, is an important feature of emphysema and is likely to be irreversible.

Physiological changes characteristic of the disease include mucus hypersecretion, airflow limitation and air trapping (leading to hyperinflation), gas exchange abnormalities, and cor pulmonale.

Systemic features of COPD, particularly in patients with severe disease, include cachexia, skeletal muscle wasting, increased risk of cardiovascular disease, anemia, osteoporosis, and depression.

Exacerbations represent a further amplification of the inflammatory response in the airways of patients with COPD, and may be triggered by infection with bacteria or viruses or by environmental pollutants.

DIAGNOSTIC APPROACH

Patients typically are seen in the fifth decade of life. A clinical diagnosis of COPD should be considered in any patient who has dyspnea, chronic cough or sputum production, and/or a history of exposure to risk factors for the disease.

Physical Examination. A number of physical signs may be present in COPD, but their absence does not exclude the diagnosis. The physical signs are not specific.

Central cyanosis, or bluish discoloration of the mucosal membranes, may be present. Chest wall abnormalities include relatively horizontal ribs, «barrel-shaped» chest, and protruding abdomen. Resting respiratory rate is often increased to more than 20 breaths per minute. Patients with COPD often have reduced breath sounds. Some patients do not wheeze on their normal tidal breathing, they do so when asked to give a forced exhalation.

The diagnosis should be confirmed by ***spirometry.***

For the diagnosis and assessment of COPD, spirometry is the gold standard as it is the most reproducible, standardized, and objective way of measuring airflow limitation. The presence of a postbronchodilator $FEV_1/FVC < 0.70$ and $FEV_1 < 80\%$ predicted confirms the presence of airflow limitation that is not fully reversible.

Bronchodilator reversibility testing in COPD. Tests should be performed when patients are clinically stable and free from respiratory infection. Patients should not have taken inhaled short-acting bronchodilators in the previous six hours, long-acting bronchodilator n the previous 12 hours, or sustainedrelease theophylline in the previous 24 hours.

FEV_1 should be measured before a bronchodilator is given. The bronchodilator should be given by metered dose inhaler through a spacer device or by nebulizer. FEV_1 should be measured again 10–15 minutes after a short-acting bronchodilator is given; 30–45 minutes after the combination.

An increase in FEV_1 that is both greater than 200 ml and 12 % above the pre-bronchodilator FEV_1 is considered significant.

Measurement of arterial blood gas tensions should be considered in all patients with FEV1 < 50 % predicted or clinical signs suggestive of respiratory failure or right heart failure.

COPD is usually a progressive disease and lung function can be expected to worsen over time, even with the best available care. Symptoms and objective measures of airflow limitation should be monitored to determine when to modify therapy and to identify any complications that may develop.

Chest X-ray. An abnormal chest X-ray is seldom diagnostic in COPD unless obvious bullous disease is present, but it is valuable in excluding alternative diagnoses and establishing the presence of significant comorbidities such as cardiac failure.

Gas Transfer for Carbon Monoxide (DLCO). A low DLCO is present in many patients with COPD. The commonly used method is the single-breath technique, which uses alveolar volume calculated from the helium dilution during a single breath test. This method underestimates alveolar volume in patients with severe COPD, producing a lower value for the DLCO. This test can be useful to distinguish patients with COPD from those with asthma, because a low DLCO excludes asthma.

Arterial blood gases are needed to confirm the degree of hypoxemia and hypercapnia that develops in patients with COPD. Hypoxemia and hypercapnia are not usually observed until the FEV1 falls below 50 % of predicted. Pulse oximetry is increasingly used to measure the level of oxygenation.

Assessment of COPD

The goals of COPD assessment are to determine the severity of the disease, its impact on patient`s health status, and the risk of future events (exacerbations, hospital admissions, death) in order to guide therapy. Assess the following aspects of the disease separately:
- Simptoms.
- Degree of airflow limitation (using spirometry).
- Risk of exacerbations.
- Comorbidities.

Assess symptoms: validated questionnaries such as the COPD Assessment Test (CAT) or the Modified British Medical Research Council (mMRC) breathlessness scale should be used to assess symptoms.

Assess degree of airflow limitation using spirometry: table 3.1 provides the classification of airflow limitation severity in COPD.

Table 3.1 — Classification of airflow limitation severity in COPD (based on post-bronchodilator FEV_1)

In patients with $FEV_1/FVC < 0,70$		
GOLD 1	*Mild*	$FEV_1 \geq 80$ % predicted
GOLD 2	*Moderate*	50 % $\leq FEV_1 < 80$ % predicted
GOLD 3	*Severe*	30 % $\leq FEV1 < 50$ % predicted
GOLD 4	*Very Severe*	$FEV1 < 30$ % predicted

Table 3.2 — Combined Assessment of COPD

When assessing risk, choose the highest risk according
to GOLD grade or exacerbation history

Risk GOLD classification of airflow limitation	1 2 — C D — ≥ 2	**Risk** Exacerbation history
	3 4 — A B — 1 0	

mMRC 0-1   mMRC ≥ 2
CAT < 10   CAT ≥ 10

Symptoms
(mMRC or CAT score)

Patient	Characteristic	Spirometric classification	Exacerbations per year	mMRC	CAT
A	Low risk Less symptoms	GOLD 1–2	≤ 1	0–1	< 10
B	Low risk More symptoms	GOLD 1–2	≤ 1	≥ 2	≥ 10
C	High risk Less symptoms	GOLD 3–4	≥ 2	0–1	< 10
D	High risk More symptoms	GOLD 3-4	≥ 2	≥ 2	≥ 10

Treatment

Management of COPD requires a multifaceted, multidisciplinary approach as described in the Global Initiative for Chronic Lung Disease or GOLD guidelines:

1. Establish a correct diagnosis and assess severity of disease with spirometry.

2. Reduce the risk for progression by encouraging smoking cessation and avoidance of other causative agents.

3. Reduce dyspnea by appropriate administration of bronchodilators.

4. Prevent and treat complications such as hypoxia and acute exacerbations.

Manage stable COPD:

• Patient education and the reduction or elimination of the effect of risk factors.

• Individualized assessment of symptoms and future risk of exacerbation should be incorporated into the management strategy for stable COPD.

• Pharmacologic therapy is the base used to prevent and control symptoms, reduce the frequency of exacerbations and improve exercise tolerance.

Bronchodilators: These medications are central to symptom management in COPD.

• Inhaled therapy is preferred.

• The choice between β_2-agonists, anticholinergics, theophylline or combination therapy depends on the availability of medications and each patient`s individual response in terms of symptom relief and side effects.

• Bronchodilators are prescribed on an as-needed or on a regular basis to prevent or reduce symptoms.

• Long-acting inhaled bronchodilators are convenient and more effective at producing maintained symptom relief than short-acting bronchodilators.

• Combining bronchodilators of different pharmacological classes may improve efficacy and decrease the risk of side effects compared to increasing the dose of a single bronchodilator.

Inhaled glucocorticosteroids: In COPD patients with FEV_1 < 60 % predicted, regular treatment with inhaled corticosteroids improves symptoms, lung function, and quality of life, and reduces the frequency of exacerbations. Inhaled corticosteroid therapy is associated with an increased risk of pneumonia. Withdrawal from treatment with corticosteroids may lead to exacerbations in some patients. Long-term monotherapy with inhaled corticosteroids is not recommended.

Oral corticosteroids: Long-term treatment is not recommended.

Phosphoddiesterase-4 inhibitors: In GOLD 3 and GOLD 4 patients with a history of exacerbations and chronic bronchitis, the phosphodiesterase-4 inhibitor roflumilast reduces exacerbations treated with oral corticosteroids. These effects are seen when roflumilast is added to long-acting bronchodilators; there are no comparison studies with inhaled corticosteroids.

Methylxanthines are less effective and less well tolerated than inhaled long-acting bronchodilators and are not recommended if those drugs are available and affordable.

Mucolytics (ambroxol, erdosteine, carbocysteine, iodinated glycerol) are used as an adjuvant treatment in the presence of viscous mucus.

Components of **pulmonary rehabilitation:** medical evaluation and management, therapeutic modalities, exercise training, education, psychosocial counseling, breathing retraining, nutritional counseling, long-term continuation. In patients with impaired exercise tolerance secondary to COPD, a rehabilitation program focusing on education and a regimen of exercise training often is quite beneficial. Most patients participating in such a program report an improved sense of wellbeing at the same time

they experience an improvement in exercise tolerance. Educating the patient about and assisting the patient with smoking cessation are absolutely critical parts of any comprehensive therapeutic program. Pharmacologic assistance to ameliorate the effects of nicotine withdrawal, using nicotine replacement therapy, bupropion, or varenicline, often is a valuable component of smoking cessation efforts. Vaccination against influenza and pneumococcus is indicated for all patients as a preventive strategy and as a component of the overall therapeutic regimen.

Table 3.3 — Pharmacologic therapy for stable COPD*

Patient group	First choice	Second choice	Alternative choice**
A	SA anthicholinergic prn or SA β_2-agonist prn	LA anthicholinergic or LA β_2-agonist or SA β_2-agonist and SA anthicholinergic	Theophylline
B	LA anthicholinergic or LA β_2-agonist	LA anthicholinergic and LA β_2-agonist	SA β_2-agonist and/or SA anthicholinergic
C	ICS + LA β_2-agonist or LA anthicholinergic	LA anthicholinergic and LA β_2-agonist	PDE-4 ihibitor SA β_2-agonist and/or SA anthicholinergic Theophylline
D	ICS + LA β_2-agonist or LA anthicholinergic	ICS and LA anthicholinergic or ICS + LA β_2-agonist and LA anthicholinergic or ICS + LA β_2-agonist and PDF-4 inhibitor or LA anthicholinergic and LA β_2-agonist or LA anthicholinergic and PDF-4 inhibitor	Carbocysteine SA β_2-agonist and/or SA anthicholinergic Theophylline

*Medication in each box are mentioned in alphabetical order and therefore not necessarily in order of preference.

**Medication in this column can be used alone or in combination with other options in the First and Second choice columns.

Glossary: SA — short-acting; LA — long-acting; ICS — inhaled corticosteroid; PDE-4 — phosphodiesterase-4; prn — when necessary.

Oxygen therapy, one of the principal nonpharmacologic treatments for patients with *Stage IV: Very Severe COPD.* The primary goal of oxygen therapy is to increase the baseline PaO_2 to at least 60 mm Hg at sea level and rest, and/or produce an SaO_2 at least 90 %, The long-term administration of oxygen (flow of 1–2 liters per minute for at least 15 hours a day) to patients with chronic respiratory failure has been shown to increase survival.

Surgical Treatments

Bullectomy is effective in reducing dyspnea and improving lung function. *Lung volume reduction surgery,* is surgical procedure in which parts of the lung are resected to reduce hyperinflation, making respiratory muscles more effective pressure generator. LVRS increases the elastic recoil pressure of the lung and thus improves expiratory flow rates. The other surgical approach to treatment of end-stage COPD is *lung transplantation.* However, this is not a practical approach for large numbers of individuals because of the resources needed, the shortage of donor organs, and the age of most patients with COPD.

Management of acute exacerbations of COPD

An exacerbation of COPD is defined as an event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variations.

An increase in the dose or frequency of inhaled short-acting bronchodilators (short-acting β_2-agonist or an anticholinergic, with both drugs used together in the event of inadequate clinical response) is the mainstay of therapy. Administering the medications by nebulization is any more effective than by a metered-dose inhaler and large-volume spacer.

Methylxanthines (theophylline or aminohylline) is currently considered second-line intravenous therapy, used when there is inadequate or insufficient response to short-acting bronchodilators.

Systemic glucocorticosteroids should be considered in addition to bronchodilators if the patient's baseline FEV1 is < 50 % predicted. A dose of 30–40 mg prednisolone per day for 10–14 days is recommended.

Patients experiencing COPD exacerbations with clinical signs of airway infection (e.g., increased sputum purulence) may benefit from antibiotic treatment.

Local resistance patterns and antibiotic policies will dictate the choice of drug, but coverage should include the common pathogens Haemophilus influenzae, Moraxella catarrhalis, and Streptococcus pneumoniae. An oral aminopenicillin, macrolide, cephalosporins — 2nd or

3rd generation or Fluoroquinolonese (Levofloxacin, Moxifloxacin) is, therefore, an appropriate empiric choice.

Oxygen should be administered in a controlled manner with monitoring of arterial blood gas tensions or saturations to avoid CO_2 retention. Venturi masks provide a more reliable FiO_2 than nasal cannulae, but the latter may be better tolerated. If non-invasive ventilation was ineffective, showed an invasive ventilation.

Increased dose and/or frequency of BRONCHODILATORS	
Systemic CORTICOSTEROIDS	O_2 +/− NIV
ANTIBIOTICS if change in sputum	
Additional therapies (e.g., theophylline)	
MECHANICAL VENTILATION	
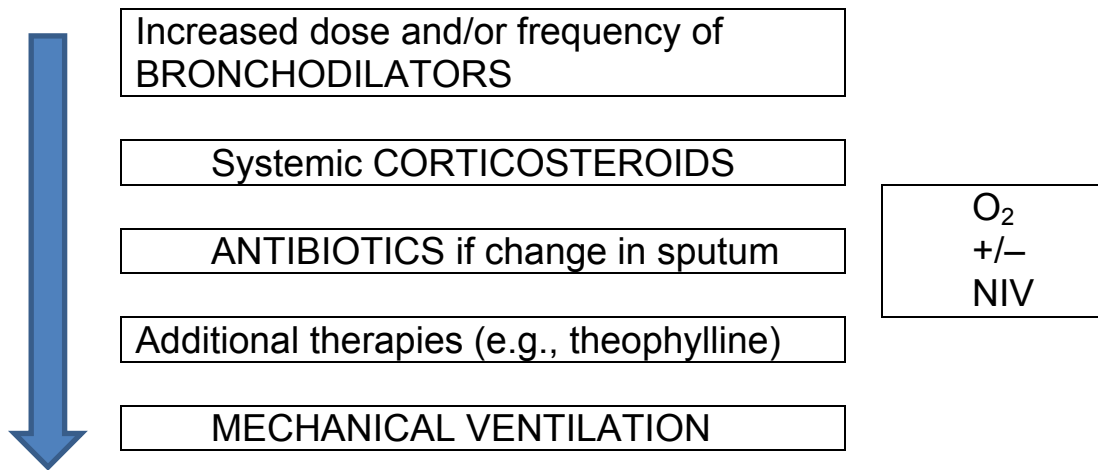
Increasing severity of exacerbation

Figure 3.1 — Stepwise therapeutic approach to COPD exacerbation

4. BRONCHIECTASIS

BRONCHIECTASIS is dilation and destruction of larger bronchi caused by chronic infection and inflammation.

Etiology
Bronchiectasis may affect many areas of the lung (diffuse bronchiectasis), or it may appear in only one or two areas (focal bronchiectasis). Diffuse bronchiectasis develops in patients with genetic, immune, or anatomic defects that affect the airways. Cystic fibrosis is the most common cause. Immunodeficiencies may also cause diffuse disease, as may rare abnormalities in airway structure. Diffuse bronchiectasis is an uncommon complication of more common conditions, such as RA or Sjögren's syndrome. Allergic bronchopulmonary aspergillosis is a hypersensitivity reaction to *Aspergillus* sp. It occurs primarily in people with asthma and less commonly in people with cystic fibrosis and can lead to bronchiectasis.

Focal bronchiectasis develops from untreated pneumonia or obstruction (eg, due to foreign bodies and tumors). Mycobacteria can cause focal bronchiectasis as well as colonize the lungs of patients with bronchiectasis due to other disorders. Some cases have no readily apparent cause.

Pathophysiology
All the causative conditions impair airway clearance mechanisms and host defenses, resulting in an inability to clear secretions, which, in turn, predisposes patients to chronic infection and inflammation. As a result of frequent infections, most commonly with *Haemophilus influenza* (35 %), *Pseudomonas aeruginosa* (31 %), *Moraxella catarrhalis* (20 %), *Staphylococcus aureus* (14 %), and *Streptococcus pneumonia* (13 %), airways become inspissated with viscous mucus containing inflammatory mediators and pathogens and slowly become dilated, scarred, and distorted. Histologically, bronchial walls are thickened by edema, inflammation, and neovascularization. Destruction of surrounding interstitium and alveoli causes fibrosis, emphysema, or both.

Superinfection with multidrug-resistant organisms, including *Mycobacterium tuberculosis*, and mycobacteria other than *M. tuberculosis* can cause recurrent exacerbations and worsen airflow limitation on pulmonary function tests. Pulmonary hypertension and right-sided heart failure may ensue because functional lung tissue decreases.

Symptoms and Signs
Symptoms characteristically begin insidiously and gradually worsen over years. The major presenting symptom of bronchiectasis is chronic cough that almost always produces large volumes of thick, tenacious, purulent sputum. Dyspnea and wheezing are common. Hemoptysis, which can be massive, is due to neovascularization of the airways from the bronchial (as opposed to pulmonary) arteries. Acute exacerbations of disease due to

new or worsened infection increase the extent of cough and the volume and purulence of sputum production. Low-grade fever may also be present.

Halitosis and abnormal breath sounds, including crackles, rhonchi, and wheezing, are typical signs of disease. Finger clubbing may also be present. In advanced cases, hypoxemia and signs of pulmonary hypertension (eg, shortness of breath, dizziness) and right-sided heart failure can occur.

Diagnosis:
- History and physical examination.
- Chest x-ray.
- High-resolution CT for confirmation.
- Pulmonary function tests for baseline function and progression of disease.
- Specific tests for suspected causes.

Diagnosis is based on a history, physical examination, and radiologic testing, beginning with a chest x-ray. Chronic bronchitis may mimic bronchiectasis clinically, but bronchiectasis is distinguished by more voluminous daily production of purulent sputum and by dilated airways on imaging studies.

Imaging: X-ray findings suggestive of bronchiectasis include scattered irregular opacities caused by mucous plugs, honeycombing, and rings and «tram lines» caused by thickened, dilated airways located perpendicular to the x-ray beam. Radiographic patterns may differ by underlying disease: Bronchiectasis due to cystic fibrosis develops predominantly in upper lobes, whereas that due to other causes is more diffuse or predominates in the lower lobes.

High-resolution CT is the test of choice for defining the extent of bronchiectasis. The test is nearly 100 % sensitive and specific. CT typically shows thickening of airways characterized by tram-track parallel lines or ring shadows representing thickened bronchial walls when imaged in cross-section. Cysts (sometimes appearing as grapelike clusters), scattered mucous plugs, and airways that are dilated > 1.5 times the diameter of nearby blood vessels can also be seen. Dilated medium-sized bronchi may extend almost to the pleurae. Atelectasis, consolidation, and decreased vascularity are nonspecific findings. A differential diagnosis of dilated airways includes bronchitis and traction bronchiectasis that occurs when pulmonary fibrosis pulls airways open.

Pulmonary function tests: Pulmonary function tests can be helpful for documenting baseline function and for following the progression of disease over time. Bronchiectasis causes airflow limitation (reduced forced expiratory volume in 1 sec [FEV_1], forced vital capacity [FVC], and FEV_1/FVC); the FEV_1 can improve in response to β-agonist bronchodilators. Lung volume measurements may be increased or decreased, and diffusing capacity for carbon monoxide (DLco) may be decreased.

Diagnosis of cause: Tests to help diagnose a cause include sputum evaluation, including staining and cultures for bacterial, mycobacterial (*Mycobacterium avium* complex and *M. tuberculosis*), and fungal (*Aspergillus*) infection. Mycobacterial superinfection is diagnosed by re-

peatedly culturing mycobacteria other than TB in high colony counts and by finding granulomas on biopsy with concurrent radiologic evidence of disease. Additional tests may include the following:

- Sweat chloride testing to diagnose cystic fibrosis (which should be done even in older patients).
- Rheumatoid factor and other serologic tests to look for connective tissue diseases.
- Immunoglobulin measurement (including IgG subclass determination), *Aspergillus* precipitins, IgE, and eosinophilia to rule out allergic bronchopulmonary aspergillosis.
- α_1-Antitrypsin levels to document α_1-antitrypsin deficiency.

When the clinical presentation suggests ciliary dyskinesia (by concurrent sinus disease and middle and lower lobe bronchiectasis with or without infertility), a nasal or bronchial epithelial sample should be obtained and examined by transmission electron microscopy for abnormal ciliary structure. A less invasive alternative is examination of sperm motility. The diagnosis of ciliary dyskinesia should be made cautiously by an experienced physician trained in specialized electron microscopic techniques because nonspecific structural defects can be present in up to 10 % of cilia in healthy patients and in patients with pulmonary disease; infection can cause transient dyskinesia; and ciliary ultrastructure may be normal in patients with primary ciliary dyskinesia syndromes characterized by abnormal ciliary function.

Bronchoscopy is indicated when an anatomic or an obstructing object or lesion is suspected.

Prognosis

Overall, prognosis is thought to be good, with about 80 % of patients having no further deterioration of lung function on the basis of bronchiectasis alone. However, cystic fibrosis patients have a median survival of 36 yr, and most patients continue to have intermittent acute exacerbations.

Treatment:

- Prevention of exacerbations with antibiotics and regular vaccinations.
- Measures to help clear secretions.
- Antibiotics for acute exacerbations.
- Sometimes surgical resection.

There is no consensus on the best approach to prevent or limit acute exacerbations. Options include daily prophylactic oral antibiotics (eg, ciprofloxacin 500 mg bid) and, in patients who have cystic fibrosis and are colonized with *P. aeruginosa,* inhaled tobramycin (300 mg bid every other month). In patients with diffuse bronchiectasis due to other causes, aerosolizedgentamicin (40 mg bid) may also be effective. Chronic therapy with azithromycin 500 mg po 3 times/wk has demonstrated efficacy in patients with cystic fibrosis; it is unclear whether macrolides are useful in other patients. The mechanism of this effect is not known and may not be due to antibiotic effect.

As with all patients with chronic pulmonary disease, annual vaccination against influenza and vaccination every 5 yr against pneumococcus is recommended.

Various techniques can facilitate clearance of secretions, including postural drainage and chest percussion, positive expiratory pressure devices, intrapulmonary percussive ventilators, pneumatic vests, and autogenic drainage (a breathing technique thought to help move secretions from peripheral to central airways). Nebulized drugs, including a mucolytic (rhDNase) or hypertonic (7 %) saline, have clinical utility in patients with cystic fibrosis. Patients should be introduced to these techniques by a respiratory therapist and should use whichever technique is most effective for them.

Additional treatment depends on the cause. Allergic bronchopulmonary aspergillosis is treated with corticosteroids and possibly with azole antifungals. Patients with immunoglobulin or α_1-antitrypsin deficiencies should receive replacement therapy.

Acute exacerbations: Acute exacerbations are treated with antibiotics and increased efforts to clear sputum from the airways with the use of bronchodilators and mucolytics. Inflammation may be treated with inhaled or oral corticosteroids. Antibiotic choice depends on whether patients have cystic fibrosis or non-cystic fibrosis bronchiectasis.

Antibiotics for non-cystic fibrosis bronchiectasis should initially cover *H. influenzae*, *P. aeruginosa*, *M. catarrhalis*, *S. aureus*, and *S. pneumonia* (eg, ciprofloxacin 500 mg po bid or levofloxacin 500 mg po once/day for 7 to 14 days) and should be adjusted according to culture results.

Antibiotic selection for cystic fibrosis exacerbations is guided by sputum culture. Routine annual sputum cultures should be done on all patients with cystic fibrosis. During childhood, common infecting organisms are *S. aureus* and *H. influenza* and quinolone antibiotics such as ciprofloxacin and levofloxacin may be used. In the later stages of cystic fibrosis, infections involve highly resistant strains of certain gram-negative organisms including *P. aeruginosa*, *Burkholderia cepacia*, and *Stenotrophomonas maltophilia*. In these patients, treatment is with multiple antibiotics (eg, tobramycin, aztreonam, ticarcillin/clavulanate, ceftazidime, cefepime). IV administration is frequently required.

Complications: Significant hemoptysis is usually treated with bronchial artery embolization, but surgical resection may be considered if pulmonary function is adequate.

Surgical resection for localized bronchiectasis is rarely needed but is considered when medical therapy has been optimized and the symptoms are intolerable. In certain patients with diffuse bronchiectasis, lung transplantation is also an option. Five-year survival rates as high as 65 to 75 % have been reported when a heart-lung or double lung transplantation is done. Pulmonary function usually improves within 6 mo, and the improvement may be sustained for at least 5 yr.

5. PULMONARY HYPERTENSION

PULMONARY HYPERTENSION is increas ed pressure in the pulmonary circulation. Pulmonary hypertension is defined as a mean pulmonary arterial pressure ≥ 25 mm Hg at rest or ≥ 35 mm Hg during exercise.

Etiology

Many conditions and drugs cause pulmonary hypertension. A small number of cases occur sporadically, unrelated to any identifiable disorder; these cases are termed idiopathic pulmonary arterial hypertension. The most common overall causes of pulmonary hypertension include:

- Left heart failure, including diastolic dysfunction.
- Parenchymal lung disease with hypoxia.
- Miscellaneous: Sleep apnea, connective tissue disorders, and pulmonary embolism.

Pulmonary hypertension is currently classified into 5 groups based on a number of pathologic, physiologic, and clinical factors. In the first group (pulmonary arterial hypertension), the primary disorder affects the small pulmonary arterioles.

Table 5.1 — Classification of Pulmonary Hypertension (Adapted from the Third WHO World Symposium on PAH, Venice, 2003)

Group	Type	Specific Disorders
1	Pulmonary arterial hypertension (PAH)	Familial PAH Idiopathic PAH Associated with PAH: • Connective tissue disorders. • HIV infection. • Portal hypertension. • Drugs or toxins. • Congenital heart disorders. • Other (eg, thyroid disorders, glycogen storage disease, Gaucher's disease, hemoglobinopathies, myeloproliferative disorders) Persistent pulmonary hypertension of the newborn Associated with significant venous or capillary involvement: • Pulmonary capillary hemangiomatosis. • Pulmonary veno-occlusive disease
2	Pulmonary hypertension with left-heart disease	Atrial or ventricular heart disorders Valvular heart disorders
3	Pulmonary hypertension associated with lung disorders, hypoxemia, or both	Alveolar hypoventilation disorders COPD Chronic exposure to high altitude Developmental abnormalities Interstitial lung disease Sleep-disordered breathing
4	Pulmonary hypertension due to chronic thrombotic or embolic disorders	Nonthrombotic pulmonary embolism (eg, tumors, parasites, foreign materials) Thromboembolic obstruction of distal or proximal pulmonary arteries
5	Miscellaneous	Compression of pulmonary vessels by adenopathy Fibrosing mediastinitis Lymphangiomatosis Pulmonary Langerhans' cell histiocytosis (granulomatosis) Sarcoidosis Tumors

Pathophysiology

Pathophysiologic mechanisms that cause pulmonary hypertension include increased pulmonary vascular resistance and increased pulmonary venous pressure. Pulmonary vascular resistance can be caused by obliteration of the pulmonary vascular bed or hypoxic vasoconstriction. Pulmonary hypertension is characterized by variable vasoconstriction, smooth muscle hypertrophy, and vascular wall remodeling. Vasoconstriction is thought to be due in part to enhanced activity of thromboxane and endothelin-1 (both vasoconstrictors) and reduced activity of prostacyclin and nitric oxide (both vasodilators). The increased pulmonary vascular pressure that results from vascular obstruction further injures the endothelium. Injury activates coagulation at the intimal surface, which may worsen the hypertension. Thrombotic coagulopathy due to increased activity of plasminogen activator inhibitor type 1 and fibrinopeptide A and decreased tissue plasminogen activator activity may also contribute. Focal coagulation at the endothelial surface should not be confused with chronic thromboembolic pulmonary hypertension, in which pulmonary hypertension is caused by organized pulmonary emboli.

In most patients, pulmonary hypertension eventually leads to right ventricular hypertrophy followed by dilation and right ventricular failure.

Symptoms and Signs

Progressive exertional dyspnea and easy fatigability occur in almost all patients. Atypical chest discomfort and exertional light-headedness or presyncope may accompany dyspnea. These symptoms are due primarily to insufficient cardiac output. Raynaud's syndrome occurs in about 10 % of patients with idiopathic pulmonary arterial hypertension; the majority are women. Hemoptysis is rare but may be fatal. Hoarseness due to recurrent laryngeal nerve compression by an enlarged pulmonary artery (ie, Ortner syndrome) also occurs rarely.

In advanced disease, signs may include right ventricular heave, widely split 2nd heart sound (S_2), an accentuated pulmonic component (P_2) of S_2, a pulmonary ejection click, a right ventricular 3rd heart sound (S_3), tricuspid murmur, and jugular vein distention. Liver congestion and peripheral edema are common late manifestations.

Diagnosis:
- Exertional dyspnea.
- Initial confirmation: Chest x-ray, spirometry, ECG, echocardiography, and CBC.
- Identification of underlying disorder: Ventilation-perfusion scan or CT angiography, pulmonary function testing, polysomnography, HIV testing, liver function testing, and antinuclear antibodies.
- Determination of severity: Right heart catheterization.

Pulmonary hypertension is suspected in patients with significant exertional dyspnea who are otherwise relatively healthy and have no history or signs of other diseases known to cause pulmonary symptoms.

Patients initially undergo chest x-ray, spirometry, and ECG to identify more common causes of dyspnea, followed by Doppler echocardiography to assess right ventricular and pulmonary artery pressures as well as to detect structural heart disease that might be causing pulmonary hypertension. CBC is obtained to document the presence or absence of polycythemia, anemia, and thrombocytopenia.

The most common x-ray finding in pulmonary hypertension is enlarged hilar vessels that rapidly prune into the periphery and a right ventricle that fills the anterior airspace on lateral view. Spirometry and lung volumes may be normal or detect mild restriction, and diffusing capacity for carbon monoxide (DLco) is usually reduced. Common ECG findings include right axis deviation, R > S in V_1, $S_1Q_3T_3$, and peaked P waves.

Additional tests are obtained as indicated to diagnose secondary causes that are not apparent clinically. These tests include

• Ventilation-perfusion scanning or CT angiography to detect thromboembolic disease.

• Pulmonary function tests to identify obstructive or restrictive lung disease.

• Serum serologic tests to gather evidence for or against rheumatologic disease.

Chronic thromboembolic pulmonary hypertension is suggested by CT or lung scan findings and is confirmed by arteriography. CT angiography is useful to evaluate proximal clot and fibrotic encroachment of the vascular lumen. Other tests, such as HIV testing, liver function tests, and polysomnography, are done in the appropriate clinical context.

When the initial evaluation detects no conditions known to be associated with pulmonary hypertension, pulmonary artery catheterization is necessary to measure right atrial and ventricular, pulmonary artery, and pulmonary artery occlusion pressures; cardiac output; and left ventricular diastolic pressure. Right-sided O_2 saturation should be measured to exclude atrial septal defect. Although finding a mean pulmonary arterial pressure of > 25 mm Hg in the absence of an underlying disorder identifies pulmonary hypertension, most patients with pulmonary arterial hypertension present with substantially higher pressure (eg, mean of 60 mm Hg). Lung biopsy, once widely done, is neither needed nor recommended because of its associated high morbidity and mortality.

Once pulmonary hypertension is diagnosed, the patient's family history should be reviewed to detect possible genetic transmission (eg, premature deaths in otherwise healthy members of the extended family). In familial pulmonary arterial hypertension, genetic counseling is needed to advise

mutation carriers of the risk of disease (about 20 %) and to advocate serial screening with echocardiography. Testing for mutations in the *BMPR2* gene in idiopathic pulmonary arterial hypertension may have a future role.

Prognosis

Untreated patients have a median survival of 2.5 yr. Cause of death is usually sudden death in the context of right ventricular failure. Five-year survival for epoprostenol -treated patients is 54 %, whereas that for the small minority of patients who respond to Ca channel blockers is >90 %. Signs predictive of poor survival include low cardiac output, higher pulmonary artery and right atrial pressures, lack of response to vasodilators, heart failure, hypoxemia, and reduced overall physical functioning. Patients with the connective tissue disorder systemic sclerosis are at high risk of pulmonary arterial hypertension and have a poor prognosis.

Treatment:

• Avoidance of activities that may exacerbate the condition (eg, cigarette smoking, use of sympathomimetics).

• Idiopathic and familial pulmonary arterial hypertension: Ca channel blockers; IV epoprostenol; inhaled, oral, or sc prostacyclin analogs; oral endothelin-receptor antagonists; and/or oral phosphodiesterase inhibitors.

• Secondary pulmonary arterial hypertension: Treatment of the underlying disorder.

• Rarely lung transplantation.

• Adjunctive therapy: Supplemental O_2, diuretics, and/or anticoagulants.

Patients are encouraged to avoid activities or circumstances that may exacerbate their condition. Examples include cigarette smoking, exposure to high altitudes, and drugs that lead to vasoconstriction, such as sympathomimetics.

6. RESPIRATORY FAILURE

RESPIRATORY FAILURE is inability of the respiratory system to maintain adequate gas exchange.

Arterial blood gas criteria for respiratory failure: P_{O_2} < 60 mm Hg or P_{CO_2} > 50 mm Hg

Causes of respiratory failure

Central drive:
- CNS-depressant drugs (e.g. barbiturates).
- Head injury.
- Cerebrovascular accident.
- Primary alveolar hypoventilation.

Airway obstruction:
- Foreign body or tumour.
- Asthma.
- COPD.

Spinal cord:
- Transection (apnoea if above C3).
- Poliomyelitis.

Chest wall
- Crush injury — flail chest.
- Kyphoscoliosis.

Lung parenchyma:
- Fibrosis.
- Emphysema.
- Pneumonia.
- Lung resection.
- Pneumothorax.
- Atelectasis.
- NRDS/ARDS

Respiratory muscles:
- Muscular dystrophies.

Peripheral nerves:
- Guillain–Barre.

Neuromuscular junction:
- Myasthenia gravis.
- Muscle relaxants.

Other:
- Cyanotic congenital heart disease.
- Pulmonary emboli.
- Pulmonary edema.

CLASSIFICATION OF RESPIRATORY FAILURE

Type I (*hypoxemic type*) — the arterial hypoxia is accompanied by a normal or low arterial Pco_2 (severe pneumonia, ARDS)

Type II (*ventilatory failure or hypercapnic/hypoxemic type*) — arterial Pco_2 is increased above 50 mmHg (depression of central nervous system ventilator control, disease of the respiratory bellows, COPD).

Acute respiratory failure

Chronic respiratory failure — there are permanent abnormalities in blood gases, which typically worsen periodically.

PATHOGENESIS OF GAS-EXCHANGE ABNORMALITIES
HYPOXEMIC RESPIRATORY FAILURE

In the patient with hypoxemic respiratory failure, two major pathophysiologic factors contribute to lowering of arterial Po_2: ventilation-perfusion mismatch and shunting. In the patient with significant ventilation-perfusion mismatch, regions with a low ventilation-to-perfusion ratio contribute relatively desaturated blood to the systemic circulation.

If an alveolus or a group of alveoli is partially filled with fluid, then a limited amount of ventilation reaches that particular area, whereas perfusion to the region may remain relatively preserved. Similarly, if an airway supplying a region of lung is diseased, either by pathology affecting the airway wall or by secretions occupying the lumen, then ventilation is limited.

When these problems become extreme, ventilation to a region of lung may be totally absent so that a true shunt exists. For example, alveoli may be completely filled with fluid, or an airway may be completely obstructed, preventing any ventilation to the involved area. Although the response of the pulmonary vasculature is to constrict and thereby limit perfusion to an underventilated or a nonventilated portion of the lung, this protective mechanism often cannot compensate fully for the loss of ventilation, and hypoxemia results.

HYPERCAPNIC/HYPOXEMIC RESPIRATORY FAILURE

In the hypercapnic form of respiratory failure, patients are unable to maintain a level of alveolar ventilation sufficient to eliminate CO_2 and to keep arterial Pco_2 within the normal range. Because ventilation is determined by a sequence of events ranging from generation of impulses by the respiratory controller to movement of air through the airways, there are several stages at which problems can adversely affect total minute ventilation. This sequence is shown in Figure 6.1, which also lists some of the disorders that can interfere at each level.

RESPIRATORY GENERATOR (CNS)	→	CHEST WALL, NEUROMUSCULAR SYSTEM	→	LUNGS, AIRWAYS

Factors potentially decreasing alveolar ventilation:

(1) Drugs
(2) Hypothyroidism
(3) Metabolic alkalosis
(4) Structural lesion(s) in CNS
(5) Idiopathic alveolar hypoventilation

(1) Kyphoscoliosis
(2) Myasthenia gravis
(3) Guillain-Barré syndrome
(4) Amyotrophic lateral sclerosis
(5) Polymyositis
(6) Cervical cord injury
(7) Muscular dystrophy
(8) Poliomyelitis
(9) Obesity
(10) Electrolyte abnormalities ($\downarrow$K, $\downarrow$PO$_4$, $\downarrow$Mg)
(11) Diaphragmatic fatigue

(1) Chronic obstructive lung disease
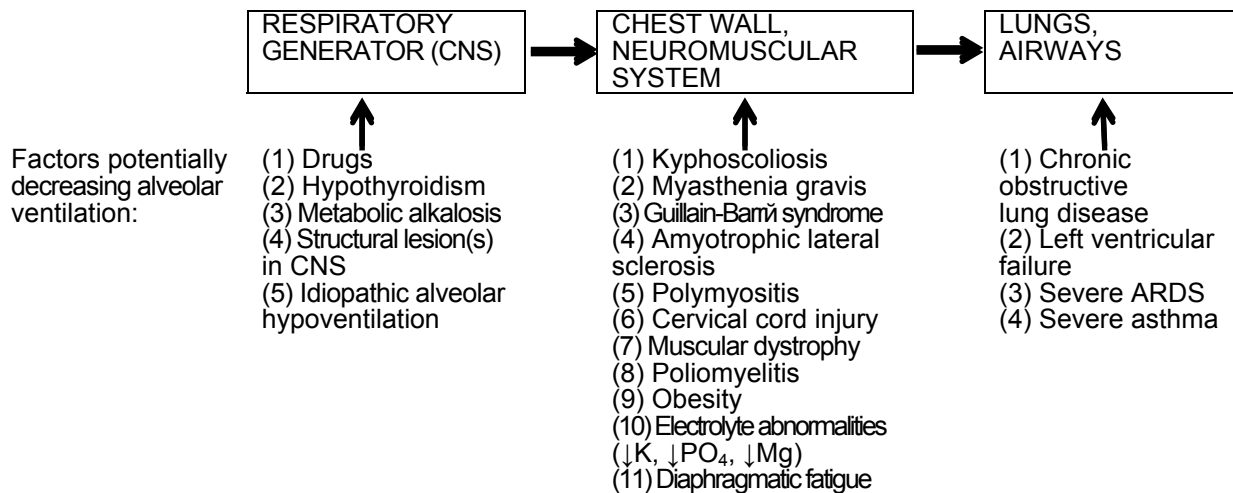(2) Left ventricular failure
(3) Severe ARDS
(4) Severe asthma

Figure 6.1 — Levels at which interference with normal ventilation give rise to alveolar hypoventilation. Factors contributing to decreased ventilation are listed under each level

Not only is the total ventilation per minute important; the «effectiveness» of the ventilation for CO_2 excretion, that is, the relative amount of alveolar versus dead space ventilation, also is important to ensure proper utilization of inspired gas. If the proportion of each breath going to dead space (i.e., ratio of volume of dead space to tidal volume [Vd/Vt]) increases substantially, then alveolar ventilation may fall to a level sufficient to cause an elevated P_{CO_2}, even if total minute ventilation is preserved. In the hypercapnic form of respiratory failure, hypoventilation also leads to a decrease in alveolar P_{O_2}. As a result, arterial P_{O_2} falls even if ventilation-perfusion matching and gas exchange at the alveolar level are well maintained. In practice, however, many of the diseases associated with alveolar hypoventilation, ranging from neuromuscular and chest wall disease to chronic airflow obstruction, are accompanied by significant ventilation-perfusion mismatch. Therefore, patients generally have two major reasons for hypoxemia: hypoventilation and ventilation-perfusion mismatch.

Table 6.1 — Effects of hypoxia and hypercapnia

	Acute	**Chronic — compensation and complications**
Low P_aO_2 (hypoxaemia/ hypoxia)	**Impaired CNS function**: irritability, confusion, drowsiness, convulsions, coma, death **Central cyanosis** (not very sensitive; may be absent in anaemia) **Cardiac arrhythmias** **Hypoxic vasoconstriction*** of pulmonary vessels	**Erythropoietin** from hypoxic kidney → **polycythaemia** →↑ oxygen carriage despite low P_aO_2 but if excessive (haematocrit >55 %) the ↑viscosity impairs tissue blood flow **Polycythaemia** → florid complexion; increased cyanosis **Pulmonary hypertension** → right ventricular hypertrophy **Fluid retention/right heart failure (cor pulmonale)** → peripheral edema/ascites/↑jugular venous pressure/enlarged liver
High P_aCO_2 (hypercapnia)	**Low arterial pH** (respiratory acidosis) **Peripheral vasodilatation**→ warm flushed skin, bounding pulse **Cerebral vasodilatation**→↑ intracranial pressure→headache, worse on waking if nocturnal ventilation↓ **Impaired CNS/muscle function**: irritability, confusion, somnolence, coma, tremor, myolonic jerks, hand flap **Cardiac arrhythmias**	**Renal compensation** (compensatory metabolic alkalosis) → ↑arterial [HCO$_3$] → arterial pH returned to near normal **Cerebrospinal fluid (CSF) compensation** →↑CSF [HCO3 –] → CSF pH returned to near normal → respiratory drive less at any given P_aCO_2 than in acute hypercapnia

7. ASTHMA

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment.

It is a common disorder that affects approximately 3 to 5 % of the population. Although asthma can occur in any age group, it is particularly common in children and young adults and probably is the most common chronic disease in these age groups.

The primary feature that patients with asthma appear to have in common is *hyperresponsiveness* of the airways, that is, an exaggerated response of airway smooth muscle to a wide variety of stimuli. The hyperresponsiveness likely is due to underlying airway inflammation with a variety of types of inflammatory cells, especially eosinophils. The particular constellation of stimuli triggering the attacks often varies among patients, but the net effect (bronchoconstriction) is qualitatively similar. Because asthma is, by definition, a disease with at least some reversibility, the patient experiences exacerbations (attacks) interspersed between intervals of diminished symptoms or symptom-free periods. During an attack, the diagnosis usually is straightforward. During a symptom-free period, the diagnosis may be more difficult to make and may require provocation or challenge tests to induce airway constriction.

ETIOLOGY AND PATHOGENESIS
RISK FACTORS FOR DEVELOPING ASTHMA

Host Factors

Genetics. A substantial proportion of patients with asthma have an underlying history of allergies (allergic rhinitis and eczema) along with accompanying markers for allergic disease, such as positive skin tests and elevated immunoglobulin E (IgE) levels. In these patients, the asthma frequently is exacerbated by exposure to various allergens to which the patients have been previously sensitized. Patients with an allergic component to their asthma often have a strong family history of asthma or other allergies, suggesting that genetic factors may play a role in the development of asthma as well as the underlying allergic diathesis (often called *atopy*). However, no simple pattern of mendelian inheritance suggesting a single gene as responsible for either atopy or asthma has been identified.

Airway hyperresponsiveness or bronchial hyperreactivity in asthma is an exaggerated response to numerous exogenous and endogenous stimuli. The mechanisms involved include direct stimulation of airway smooth muscle and indirect stimulation by pharmacologically active substances from mediator-secreting cells such as mast cells or nonmyelinated sensory neurons. The degree of airway hyperresponsiveness generally correlates with the clinical severity of asthma.

Airway inflammation and epithelial injury may contribute to nonspecific bronchial hyperresponsiveness.

Obesity. Asthma is more frequently observed in obese subjects (Body Mass Index > 30 kg/m^2). Obese people with asthma have lower lung function and more co-morbidities compared with normal weight people with asthma.

Sex. Male sex is a risk factor for asthma in children. Prior to the age of 14, asthma prevails in boys. In adults the prevalence of asthma is greater in women than in men. However, lung size is smaller in males than in females at birth but larger in adulthood.

Environmental factors

Allergen Exposure. The pathogenetic mechanisms leading to bronchoconstriction are best defined for allergen-induced asthma. Allergens to which an asthmatic person may be sensitized are widespread throughout nature. Although patients and clinicians often first consider seasonal outdoor allergens, such as pollen, many indoor allergens may play a more critical role. These allergens include antigens from house dust mites (*Dermatophagoides* and others), domestic animals, and cockroaches.

Inhaled Irritants, such as cigarette smoke, inorganic dusts, and environmental pollutants, are common precipitants of bronchoconstriction in asthmatic persons. These airborne irritants appear to stimulate *irritant receptors* located primarily in the walls of the larynx, trachea, and large bronchi. Stimulation of the receptors initiates a reflex arc that travels to the central nervous system and back to the bronchi via the vagus nerve. This efferent vagal stimulation of the bronchi completes the reflex arc and induces bronchoconstriction.

Respiratory Tract Infection is a factor for patients with nonallergic as well as allergic asthma. Viral infections are the most common causes in this category, but bacterial infections of the tracheobronchial tree also can be implicated. The mechanism by which respiratory infections precipitate bronchoconstriction in asthmatic persons is not entirely clear but likely is related to epithelial damage and airway inflammation. Potential consequences of epithelial injury include release of mediators from inflammatory cells, stimulation of irritant receptors, and nonspecific bronchial hyperresponsiveness.

Exercise can frequently provoke bronchoconstriction in patients with hyperreactive airways. The crucial factor in the pathogenesis appears to be heat movement from the airway wall, resulting in cooling of the airway. During exercise, individuals have a high minute ventilation, and the large amounts of relatively cool and dry inspired air must be warmed and humidified by the tracheobronchial mucosa. When the air is warmed and humidified, water evaporates from the epithelial surface, resulting in cooling of the airway epithelium. The phenomenon of exercise-induced bronchoconstriction can be reproduced by having an asthmatic person voluntarily breathe cold, dry air at a high minute ventilation. Inhalation of warm, saturated air at the same minute ventilation does not produce a similar effect. The mechanism that links airway cooling and drying with bronchoconstriction is less clear. Alteration of the ionic environment after drying of the mucosa, mediator release, hyperemia of the mucosa following airway rewarming, and stimulation of irritant receptors all have been proposed as mechanisms, but none is universally accepted.

As might be expected from the description of exercise-induced bronchoconstriction, inhalation of cold air during the winter months can be responsible for asthma exacerbations or worsening of symptoms in selected patients. The mechanism of airway narrowing in these patients following inhalation of cold air is also believed to be due to airway cooling and drying and therefore is analogous to the mechanism of exercise- induced bronchoconstriction.

PATHOLOGY MECHANISMS OF ASTHMA

Asthma is an inflammatory disorder of the airways, which involves several inflammatory cells and multiple mediators that result in characteristic pathophysiological changes.

Airway Inflammation in Asthma

The clinical spectrum of asthma is highly variable, and different cellular patterns have been observed, but the presence of airway inflammation remains a consistent feature. The airway inflammation in asthma is persistent even though symptoms are episodic, and the relationship between the severity of asthma and the intensity of inflammation is not clearly established. The pathologic changes are present at many levels of the tracheobronchial tree, from large airways down to the peripheral airways less than 2 mm in diameter. The pattern of inflammation in the airways appears to be similar in all clinical forms of asthma, whether allergic, non-allergic, or aspirin-induced, and at all ages.

Inflammatory cells. The characteristic pattern of inflammation found in allergic diseases is seen in asthma, with activated mast cells, increased numbers of activated eosinophils, and increased numbers of T

cell receptor invariant natural killer T cells and T helper 2 lymphocytes (Th2), which release mediators that contribute to symptoms. Structural cells of the airways also produce inflammatory mediators, and contribute to the persistence of inflammation in various ways.

Mast cells: Activated mucosal mast cells release bronchoconstrictor mediators (histamine, cysteinyl leukotrienes, prostaglandin D2). These cells are activated by allergens through high-affinity IgE receptors, as well as by osmotic stimuli (accounting for exercise-induced bronchoconstriction). Increased mast cell numbers in airway smooth muscle may be linked to airway hyperresponsiveness.

Eosinophils, present in increased numbers in the airways, release basic proteins that may damage airway epithelial cells. They may also have a role in the release of growth factors and airway remodeling.

T lymphocytes, present in increased numbers in the airways, release specific cytokines, including IL-4, IL-5, IL-9, and IL-13, that orchestrate eosinophilic inflammation and IgE production by B lymphocytes.

Dendritic cells sample allergens from the airway surface and migrate to regional lymph nodes, where they interact with regulatory T cells and ultimately stimulate production of Th2 cells from naive T cells.

Macrophages are increased in number in the airways and may be activated by allergens through low-affinity IgE receptors to release inflammatory mediators and cytokines that amplify the inflammatory response.

Neutrophil numbers are increased in the airways and sputum of patients with severe asthma and in smoking asthmatics.

Airway epithelial cells sense their mechanical environment, express multiple inflammatory proteins in asthma, and release cytokines, chemokines, and lipid mediators. Viruses and air pollutants interact with epithelial cells.

Airway smooth muscle cells express similar inflammatory proteins to epithelial cells.

Endothelial cells of the bronchial circulation play a role in recruiting inflammatory cells from the circulation into the airway.

Fibroblasts and myofibroblasts produce connective tissue components, such as collagens and proteoglycans, that are involved in airway remodeling.

Airway nerves are also involved. Cholinergic nerves may be activated by reflex triggers in the airways and cause bronchoconstriction and mucus secretion. Sensory nerves, which may be sensitized by inflammatory stimuli including neurotrophins, cause reflex changes and symptoms such as cough and chest tightness, and may release inflammatory neuropeptides.

Inflammatory mediators. Over 100 different mediators are now recognized to be involved in asthma and mediate the complex inflammatory response in the airways.

Chemokines are important in the recruitment of inflammatory cells into the airways and are mainly expressed in airway epithelial cells

Cysteinyl leukotrienes are potent bronchoconstrictors and proinflammatory mediators mainly derived from mast cells and eosinophils.

Cytokines orchestrate the inflammatory response in asthma and determine its severity. Key cytokines include IL-4, IL-5, IL-9, IL-13, and TNF-α.

Histamine is released from mast cells and contributes to bronchoconstriction and to the inflammatory response.

Nitric oxide (NO), a potent vasodilator, is produced predominantly from the action of inducible nitric oxide synthase in airway epithelial cells.

Prostaglandin D2 is a bronchoconstrictor derived predominantly from mast cells and is involved in Th2 cell recruitment to the airways.

Structural changes in the airways. In addition to the inflammatory response, there are characteristic structural changes, often described as airway remodeling, in the airways of asthma patients. Subepithelial fibrosis results from the deposition of collagen fibers and proteoglycans under the basement membrane and is seen in all asthmatic patients, including children, even before the onset of symptoms but may be influenced by treatment. Fibrosis occurs in other layers for the airway wall, with deposition of collagen and proteoglycans.

Airway smooth muscle increases, due both to hypertrophy (increased size of individual cells) and hyperplasia (increased cell division), and contributes to the increased thickness of the airway wall.

Blood vessels in airway walls proliferate the influence of growth factors such as vascular endothelial growth factor (VEGF) and may contribute to increased airway wall thickness.

Mucus hypersecretion results from increased numbers of goblet cells in the airway epithelium and increased size of submucosal glands.

Pathophysiology

Airway narrowing is the final common pathway leading to symptoms and physiological changes in asthma. Several factors contribute to the development of airway narrowing in asthma:

• Airway smooth muscle contraction.
• Airway edema.
• Airway thickening due to structural changes (remodeling).
• Mucus hypersecretion.

The presence of histologic abnormalities presumably contributes to the nonspecific bronchial hyperresponsiveness in patients. Airway hyperresponsiveness, the characteristic functional abnormality of asthma, results in airway narrowing in a patient with asthma in response to a stimu-

lus that would be innocuous in a normal person In turn, this airway narrowing leads to variable airflow limitation and intermittent symptoms.

Acute exacerbations. Transient worsening of asthma may occur as a result of exposure to risk factors for asthma symptoms, or triggers.

Table 7.1 — Factors that may exacerbate asthma (trigger factors)

Factor	Comment
Smoking	Active and passive
Infections	Especially rhinoviruses, respiratory syncytial virus, influenza virus
Exercise	Especially on cold, dry days
Changes in the weather	Thunderstorms
Pollution	Ozone and sulfur dioxide
Allergens	Pet allergens, house dust and house dust mite, cockroach allergens, pollens
Drugs	Aspirin, nonsteroidal anti-inflammatory agents, β-blockers (oral and ophthalmic)
Occupational factors	Dusty work places, «cold rooms»

CLINICAL FEATURES

Onset of asthma occurs most frequently during childhood and young adulthood, although asthma can develop for the first time in older patients. In many patients, particularly those in whom asthma started before age 16 years, the disease eventually regresses, and patients are no longer subject to repeated episodes of reversible airway obstruction.

The symptoms most commonly noted by patients during an exacerbation of asthma are cough, dyspnea, wheezing, and chest tightness. Patients do not necessarily have a classic presentation with several or all of these complaints but may merely have an unexplained cough or breathlessness on exertion. In some cases, patients can clearly identify a precipitating factor for an attack, such as exposure to an all ergen, respiratory tract infection, exercise, exposure to cold air, emotional stress, or exposure to irritating dusts, fumes, or odors. In other cases, no precipitant can be identified. Exposures in the workplace, related to proteins or other chemicals to which the patient may be sensitized, are important precipitants in a subgroup of patients who are said to have *occupational asthma.* Some asthmatic persons are particularly sensitive to ingestion of aspirin, which is believed to favor production of leukotrienes from arachidonic acid. Some patients with aspirin sensitivity also have nasal polyps, leading to a well-recognized triad of asthma, aspirin sensitivity, and nasal polyposis (sometimes referred to as *triad asthma* or *Samter's syndrome*). Other nonsteroidal anti-inflammatory drugs (which also inhibit the cyclooxygenase enzyme) also can produce bronchoconstriction in patients who are aspirin sensitive.

On examination, patients experiencing an asthma attack usually have tachypnea and, on auscultation of the chest, prolonged expiration and evidence of wheezing. The wheezing is generally more prominent

during expiration than inspiration and may be triggered by having the patient exhale forcefully. Although the tendency is to equate wheezing and asthma, the presence of wheezing does not necessarily indicate a diagnosis of asthma. Wheezing reflects only airflow through narrowed airways; it also can be seen in such diverse disorders as congestive heart failure and chronic obstructive pulmonary disease or in the case of a foreign body in the airway. On the other hand, not all asthmatic persons wheeze. It is a common observation that severe asthma may be associated with no wheeze at all if airflow is too impaired to generate an audible wheeze.

During a particularly severe attack that is refractory to treatment with bronchodilators, persons with asthma are said to be in *status asthmaticus.* These patients present difficult therapeutic challenges, may require assisted ventilation, and may even die as a result of the acute attack.

The overall severity of an individual's asthma can be characterized on the basis of the frequency of exacerbations, nocturnal symptoms, and magnitude of abnormality and variability in pulmonary function. The features used to define four categories of severity (mild intermittent asthma, mild persistent asthma, moderate persistent asthma, and severe persistent asthma) are listed in Table 5-2.

DIAGNOSTIC APPROACH

A clinical history of reversible episodes of bronchoconstriction often is crucial to the diagnosis of asthma. Other helpful features in the history include other evidence for atopy (e.g., hay fever or eczema) or a family history of allergies or asthma. Physical examination demonstrating wheezes during an attack often provides confirmatory evidence for airway obstruction.

The chest radiograph, although sometimes useful for ruling out other causes of wheezing or complications of asthma, is generally not particularly helpful in the diagnosis.

It usually shows normal findings but may demonstrate hyperinflation with relatively large lung volumes.

If the patient is producing sputum, microscopic examination of the sputum frequently shows many eosinophils on the smear. An increased percentage of eosinophils in peripheral blood also is common, even when the asthma has no clear relationship to allergies.

The clinical usefulness of skin testing and inhalation testing with allergens in an attempt to identify antigens to which the patient is sensitized is controversial. Unfortunately, these tests do not necessarily correlate with each other and do not establish that antigens causing positive test results are responsible for exacerbations of asthma.

Although the diagnosis of asthma usually is made on the basis of clinical features, spirometry, and response to therapy, other types of provocation tests are sometimes used to make or confirm the diagnosis of asthma.

These tests rely on the principle that asthmatic persons have hyperreactive airways. Therefore, when tested with inhalation of methacholine (a cholinergic agent) or histamine, persons with asthma respond with bronchoconstriction to comparatively small doses of either agent. Inhalation of cold air at high minute ventilations with Pco_2 kept constant (termed *isocapnic hyperpnea*) also can be used as a challenge test to induce transient bronchoconstriction in patients in whom the diagnosis of asthma is uncertain.

Measurement of pulmonary function, especially FEV1 and FVC, is particularly useful in the patient with suspected or known asthma. Documentation of reversible airflow obstruction, either during attacks or with a challenge test, frequently is sufficient to make the diagnosis. In practice, the diagnosis of asthma is most commonly made by the history of episodic dyspnea, wheezing, or cough, with documentation of reversible airflow obstruction by pulmonary function testing.

Patients can conveniently test their own pulmonary function through measurement of the peak expiratory flow rate. Such testing is particularly useful for monitoring the course of the disease and alerting the patient to adjust the medication regimen, seek attention from a physician, or both. In addition, the efficacy of treatment or changes in the therapeutic regimen can readily be assessed by serial measurement of the peak expiratory flow rate.

CLASSIFICATION OF ASTHMA

Asthma Severity

Asthma by severity based on the level of symptoms, airflow limitation, and lung function variability has into four categories:

Intermittent:
- Symptoms less than once a week.
- Brief exacerbations.
- Nocturnal symptoms not more than twice a month.
- FEV1 or PEF ≥ 80 % predicted.
- PEF or FEV1 variability < 20 %.

Mild Persistent:
- Symptoms more than once a week but less than once a day.
- Exacerbations may affect activity and sleep.
- Nocturnal symptoms more than twice a month.
- FEV1 or PEF ≥ 80 % predicted.
- PEF or FEV1 variability < 20–30 %.

Moderate Persistent:
- Symptoms daily.
- Exacerbations may affect activity and sleep.
- Nocturnal symptoms more than once a week.

- Daily use of inhaled short-acting — 2-agonist.
- FEV1 or PEF 60–80 % predicted.
- PEF or FEV1 variability > 30 %.

Severe Persistent:
- Symptoms daily.
- Frequent exacerbations.
- Frequent nocturnal asthma symptoms.
- Limitation of physical activities.
- FEV1 or PEF ≤ 60 % predicted.
- PEF or FEV1 variability > 30 %.

Classification of asthma by severity is useful when decisions are being made about management at the initial assessment of a patient.

Asthma Control

The term control may indicate disease prevention, or even cure. However, in asthma, where neither of these are realistic options at present, it refers to control of the manifestations of disease. Ideally this should apply not only to clinical manifestations, but to laboratory markers of inflammation and pathophysiological features of the disease as well.

Table 7.2 — Levels of Asthma Control

Characteristic	Controlled (All of the following)	Partly Controlled (Any measure present in any week)	Uncontrolled
Daytime symptoms	None (twice o less/week)	More than twice/week	Three or more features of partly controlled asthma present in any week
Limitations of activities	None	Any	
Nocturnal symptoms/awakening	None	Any	
Need for reliever/rescue treatment	None (twice or less/week)	More than twice/week	
Lung function (PEF or FEV1)	Normal	<80 % predicted or personal best (if known)	
Exacerbations	None	One or more/year	One in any week

TREATMENT

Medications to treat asthma can be classified as controllers and relievers. Controllers are medications taken daily on a long-term basis to keep asthma under clinical control chiefly through their anti-inflammatory effects. Relievers are medications used on an as-needed basis that act quickly to reverse bronchoconstriction and relieve its symptoms.

Controller medications
Inhaled glucocorticosteroids

Inhaled glucocorticosteroids are currently the most effective anti-inflammatory medications for the treatment of persistent asthma. Studies

have demonstrated their efficacy in reducing asthma symptoms, improving quality of life, improving lung function, decreasing airway hiperresponsiveness, controlling airway inflammation, reducing frequency and severity of exacerbations, and reducing asthma mortality. However, they do not cure asthma, and when they are discontinued deterioration of clinical control follows within weeks to months in a proportion of patients.

Most of the benefit from inhaled glucocorticosteroids is achieved in adults at relatively low doses, equivalent to 400µg of budesonide per day.

Table 7.3 — Estimated equipotent daily doses of inhaled glucocorticosteroids

Drug	Low daily dose (µg)	Medium daily dose (µg)	High Daily Dose (µg)
Beclomethasone dipropionate	200–500	>500–1000	>1000–2000
Budesonide	200–400	>400–800	>800–1600
Ciclesonide	80–160	>160–320	>320–1280
Flunisolide	500–1000	>1000–2000	>2000
Fluticasone	100–250	>250–500	>500–1000
Mometasone furoate	200–400	>400–800	>800–1200
Triamcinolone acetonide	400–1000	>1000–2000	>2000

Leukotriene modifiers

Leukotriene modifiers have a small and variable bronchodilatator effect, reduce symptoms including cough improve lung function, and reduce airway inflammation and asthma exacerbations. They may be used as an alternative treatment for adult patients with mild persistent asthma, and some patients with aspirin-sensitive asthma respond well to leukotriene modifiers. However, when used alone as controller, the effect of leukotriene modifiers are generally less than that of low doses of inhaled glucocorticosteroids, and, in patients already on inhaled glucocorticosteroids, leukotriene modifiers cannot substitute for this treatment without risking the loss of asthma control. Leukotriene modifiers used as add-on therapy may reduce the dose of inhaled glucocorticosteroids required by patients with moderate to severe asthma.

Side effects — Leukotriene modifiers are well tolerated, and few if any class-related effects have so far been recognized.

Long-acting inhaled β_2-agonists

Long-acting inhaled β_2-agonists, including formoterol and salmeterol, should not be used as monotherapy. They are most effective when combined with inhaled glucocorticosteroids. This greater efficacy of combination treatment has led to the development of fixed combination inhalers that deliver both glucocorticosteroid and long-acting β_2-agonist simultaneously (fluticasone propionate plus salmeterol, budesonide plus formoterol).

Theophylline

Role in therapy — Theophylline is a bronchodilator and, when given in a lower dose, has modest anti-inflammatory properties. It may provide benefit as add-on therapy in patients who do not achieve control on in-

haled glucocorticosteroids alone. Additionally in such patients the withdrawal of sustained-release theophylline has been associated with deterioration of control. As add-on therapy, theophylline is less effective than long-acting inhaled β_2-agonists.

Cromones: sodium cromoglycate and nedocromil sodium

The role of sodium cromoglycate and nedocromil sodium in long-term treatment of asthma in adults is limited. Their anti-inflammatory effect is weak and they are less effective than a low dose of inhaled glucocorticosteroid.

Long-acting oral β_2-agonists

Role in therapy — Long acting oral β_2-agonists include slow release formulations of salbutamol, terbutaline, and bambuterol, a prodrug that is converted to terbutaline in the body. They are used only on rare occasions when additional bronchodilation is needed.

Anti-IgE

Role in therapy — Anti-IgE (omalizumab) is a treatment option limited to patients with elevated serum levels of IgE. Its current indication is for patients with severe allergic asthma who are uncontrolled on inhaled glucocorticosteroids.

Systemic glucocorticosteroids

Role in therapy — Long-term oral glucocorticosteroid therapy (that is, for periods longer than two weeks as a glucocorticosteroid "burst") may be required for severely uncontrolled asthma, but its use is limited by the risk of significant adverse effects.

Allergen-specific immunotherapy

Role in therapy — The role of specific immunotherapy in adult asthma is limited. Appropriate immunotherapy requires the identification and use of a single well-defined clinically relevant allergen. The later is administered in progressively higher doses in order to induce tolerance. The efficacy of this therapy in asthma in reducing symptom scores and medication requirements, and improving allergen-specific and non-specific airway hyperresponsiveness.

Reliever Medications

Reliever medications act quickly to relieve bronchoconstriction and its accompanying acute symptoms.

Rapid-acting inhaled β_2-agonists

Role in therapy — Rapid-acting inhaled β_2-agonists are the medications of choice for relief of bronchospasm during acute exacerbations of asthma and for the pretreatment of exercise-induced bronchoconstriction. Rapid-acting inhaled β_2-agonists should be used only on an as-needed basis at the lowest dose and frequency required.

Systemic glucocorticosteroids

Role in therapy — Although systemic glucocorticosteroids are not usually thought of as reliever medications, they are important in the treatment of severe acute exacerbations. The main effects of systemic glucocorticosteroids in acute asthma are only evident after 4 to 6 hours. Oral therapy is preferred and is as effective as intravenous hydrocortisone. A typical short course of oral glucocorticosterods for an exacerbation is 40–50 mg prednisolone given daily for 5 to 10 days depending on the severity of the exacerbation. When symptoms have subsided and lung function has approached the patient's personal best value, the oral glucocorticosteroids can be stopped or tapered, provided that treatment with inhaled glucocorticosteroids continues.

Level of Control	Reduce ⇅ Increase	Treatment Action
Controlled		Maintain and find lowest controlling step
Partly controlled		Consider stepping up to gain control
Uncontrolled		Step up until controlled
Exacerbation		Treat as exacerbation

← **Reduce**   **Treatment Steps**   **Increase** →

	Step 1	Step 2	Step 3	Step 4	Step 5
		Asthma education Environmental control			
As needed rapidacting β2-agonist	As needed rapid-acting β2-agonist				
	Select one	Select one	Add one or more	Add one or both	
Controller options	Low-dose inhaled ICS*	Low-dose ICS plus long-acting β2-agonist	Medium-or high-dose ICS plus long-acting β2-agonist	Oral glucocorticosteroid (lowest dose)	
	Leukotriene modifier U	Medium-or high-dose ICS	Leukotriene modifier	Anti-IgE treatment	
		Low-dose ICS plus leukotriene modifier	Sustained release theophylline		
		Low-dose ICS plus sustained release theophylline			

* ICS = inhaled glucocorticosteroids
U = Receptor antagonist or synthesis inhibitors

Alternative reliever treatments include inhaled anticholinergics, short-acting oral β2-agonists*, some long-acting* β2-agonists*, and short-acting theophylline. Regular dosing with short and long-acting* β2-agonist *is not advised unless accompanied by regular use of an inhaled glucocorticosteroid.*

Figure 7.1 — Management Approach Based On Control

Anticholinergics

Role in therapy — Anticholinergic bronchodilators used in asthma include ipratropium bromide and oxitropium bromide. Inhaled ipratropium bromide is a less effective reliever medication in asthma than rapid-acting inhaled β_2-agonists. it is recognized as an alternative bronchodilator for patients who experience such adverse effects as tachycardia, arrhythmia, and tremor from rapidacting β_2-agonists.

Theophylline

Role in therapy — Short-acting theophylline may be considered for relief of asthma symptoms. The role of theophylline in treating exacerbations remains controversial. Short-acting theophylline may provide no additive bronchodilator effect over adequate doses of rapid-acting $\beta2$-agonists, but it may benefit respiratory drive.

ASTHMA MANAGEMENT AND PREVENTION

The recommendations for asthma management are laid out in five interrelated components of therapy:

1. Develop Patient/Doctor Partnership.
2. Identify and Reduce Exposure to Risk Factors.
3. Assess, Treat, and Monitor Asthma.
4. Manage Asthma Exacerbations.
5. Special Considerations.

The effective management of asthma requires the development of a partnership between the person with asthma and his or her health care professional(s) The aim of this partnership is guided selfmanagement — that is, to give people with asthma the ability to control their own condition with guidance from health care professionals. The partnership is formed and strengthened as patients and their health care professionals discuss and agree on the goals of treatment, develop a personalized, written self-management plan including self-monitoring, and periodically review the patient's treatment and level of asthma control.

IDENTIFY AND REDUCE EXPOSURE TO RISK FACTORS

Asthma exacerbations may be caused by a variety of risk factors, sometimes referred to as «triggers», including allergens, viral infections, pollutants, and drugs. Reducing a patient's exposure to some categories of risk factors (e.g., smoking cessation, reducing exposure to secondhand smoke, reducing or eliminating exposure to occupational agents known to cause symptoms, and avoiding foods/additives/ drugs known to cause symptoms) improves the control of asthma and reduces medication needs.

Table 7.4 — Severity of Asthma Exacerbations*

	Mild	Moderate	Severe	Respiratory arrest imminent
Breathless	Walking Can lie down	Talking Infan — softer shorter cry; difficulty feeding Prefers sitting	At rest Infant stops feeding Hunched forward	
Talks in	Sentences	Phrases	Words	
Alertness	May be agitated	Usually agitated	Usually agitated	Drowsy or confused
Respiratory rate	Increased	Increased	Often > 30/min	
Accessory muscles and suprasternal retractions	Usually not	Usually	Usually	Paradoxical thoraco-abdominal movement
Wheeze	Moderate, often only end expiratory	Loud	Usually loud	Absence of wheeze
Pulse/min.	< 100	100-120	>120	Bradycardia
Pulsus paradoxus	Absent < 10 mm Hg	May be present 10-25 mm Hg	Often present > 25 mm Hg (adult) 20–40 mm Hg (child)	Absence suggests respiratory muscle fatigue
PEF after initial bronchodilator % predicted or % personal best	Over 80%	Approx. 60-80%	< 60% predicted or personal best (< 100 L/min adults) or response lasts < 2hrs	
PaO_2 (on air)† and/or $PaCO_2$†	Normal Test not usually Necessary < 45 mm Hg	> 60 mm Hg < 45 mm Hg	< 60 mm Hg Possible cyanosis > 45 mm Hg; Possible respiratory failure (see text)	
SaO_2% (on air)†	> 95%	91-95%	< 90%	
	Hypercapnea (hypoventilation) develops more readily in young children than in adults and adolescents			

* Note: The presence of several parameters, but not necessarily all, indicates the general classification of the exacerbation.
† Note: Kilopascals are also used internationally; conversion would be appropriate in this regard.

Initial Assessment
• History, physical examination (auscultation, use of accessory muscles, heart rate, respiratory rate, PEF or FEV1, oxygen saturation, arterial blood gas if patient in extremis)

Initial Treatment
• Oxygen to achieve O2 saturation ε 90 % (95 % in children)
• Inhaled rapid-acting _2-agonist continuously for one hour.
• Systemic glucocorticosteroids if no immediate response, or if patient recently took oral glucocorticosteroid, or if episode is severe.
• Sedation is contraindicated in the treatment of an exacerbation.

Reassess after 1 Hour
Physical Examination, PEF, O2 saturation and other tests as needed

Criteria for Moderate Episode:
• PEF 60–80 % predicted/personal best
• Physical exam: moderate symptoms, accessory muscle use
Treatment:
• Oxygen
• Inhaled β2-agonist and inhaled anticholinergic every 60 min
• Oral glucocorticosteroids
• Continue treatment for 1-3 hours, provided there is improvement

Criteria for Severe Episode:
• History of risk factors for near fatal asthma
• PEF < 60% predicted/personal best
• Physical exam: severe symptoms at rest, chest retraction
• No improvement after initial treatment
Treatment:
• Oxygen
• Inhaled β2-agonist and inhaled anticholinergic
• Systemic glucocorticosteroids
• Intravenous magnesium

Reassess after 1–2 Hours

Good Response within 1–2 Hours:
• Response sustained 60 min after last treatment
• Physical exam normal: No distress
• PEF > 70%
• O_2 saturation > 90%

Incomplete Response within 1–2 Hours:
• Risk factors for near fatal asthma
• Physical exam: mild to moderate signs
• PEF < 60%
• O_2 saturation not improving

Admit to Acute Care Setting
• Oxygen
• Inhaled β2-agonist ± anticholinergic
• Systemic glucocorticosteroid
• Intravenous magnesium
• Monitor PEF, O_2 saturation, pulse

Poor Response within 1–2 Hours:
• Risk factors for near fatal asthma
• Physical exam: symptoms severe, drowsiness, confusion
• PEF < 30%
• PCO_2 > 45 mm Hg
• $P O_2$ < 60mm Hg

Admit to Intensive Care
• Oxygen
• Inhaled β2-agonist + anticholinergic
• Intravenous glucocorticosteroids
• Consider intravenous β2-agonist
• Consider intravenous theophylline
• Possible intubation and mechanical ventilation

Reassess at intervals

Improved: Criteria for Discharge Home
• PEF > 60 % predicted/personal best
• Sustained on oral/inhaled medication

Home Treatment:
• Continue inhaled β2-agonist
• Consider, in most cases, oral glucocorticosteroids
• Consider adding a combination inhaler
• Patient education: Take medicine correctly
                Review action plan
                Close medical follow-up

Poor Response (see above):
• Admit to Intensive Care
Incomplete response in 6–12 hours (see above)
• Consider admission to Intensive Care if no improvement within 6-12 hours
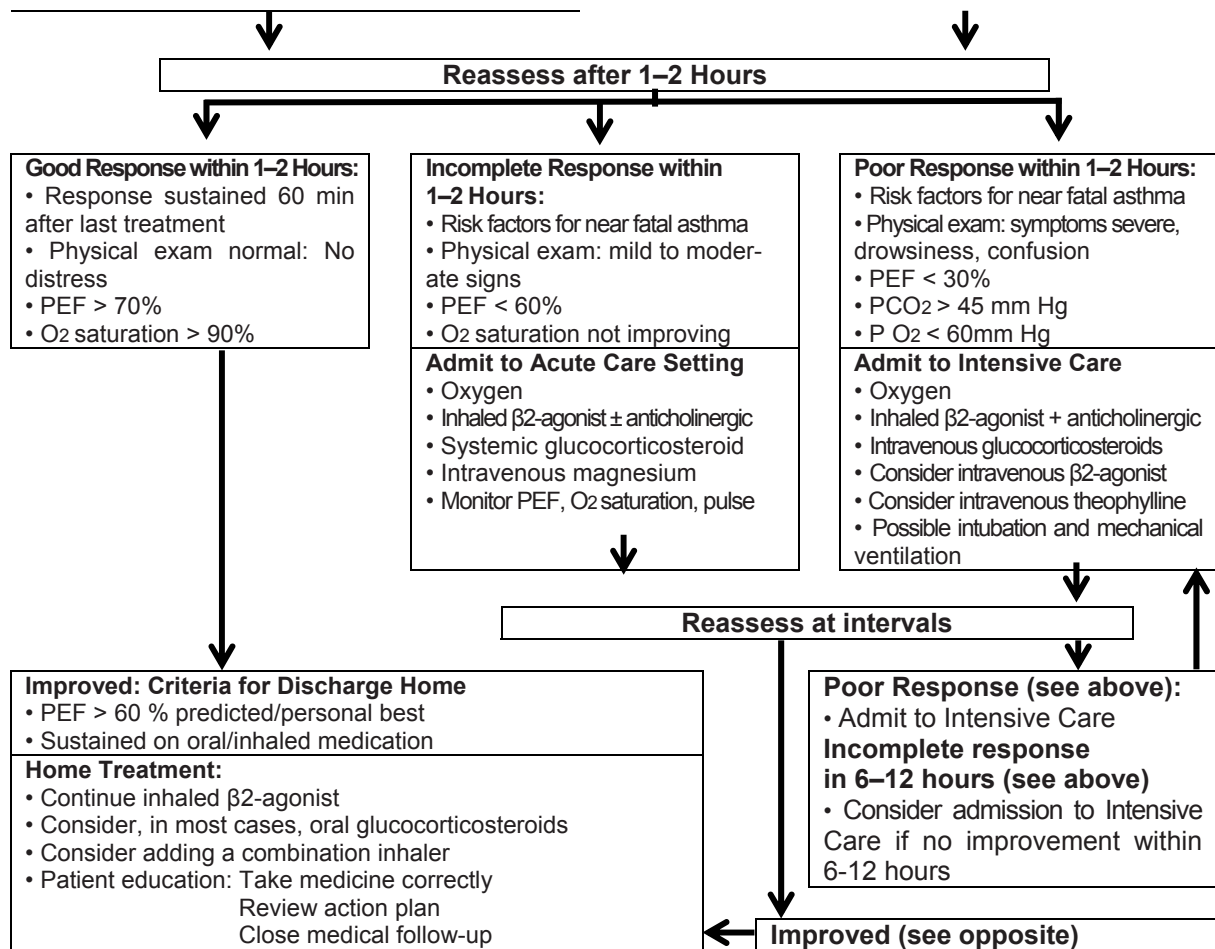
Improved (see opposite)

Figure 7.2 — Management of Asthma Exacerbations in Acute Care Setting

ASSESS, TREAT, AND MONITOR ASTHMA

The goal of asthma treatment, to achieve and maintain clinical control If asthma is not controlled on the current treatment regimen, treatment should be stepped up until control is achieved. When control is maintained for at least three months, treatment can be stepped down. In treatment-naive patients with persistent asthma, treatment should be started at *Step 2*, or, if very symptomatic (uncontrolled), at *Step 3*. For *Steps 2* through *5*, a variety of controller medications are available. At each treatment step, reliever medication should be provided for quick relief of symptoms as needed. Ongoing monitoring is essential to maintain control and to establish the lowest step and dose of treatment to minimize cost and maximize safety.

MANAGE ASTHMA EXACERBATIONS

Exacerbations of asthma (asthma attacks or acute asthma) are episodes of progressive increase in shortness of breath, cough, wheezing, or chest tightness, or some combination of these symptoms. The severity of the exacerbation determines the treatment administered.

Bronchodilators. For mild to moderate exacerbations, repeated administration of rapid-acting inhaled β2-agonists (2 to 4 puffs every 20 minutes for the first hour) is usually the best and most cost-effective method of achieving rapid reversal of airflow limitation. After the first hour, the dose of β2-agonist required will depend on the severity of the exacerbation. Mild exacerbations respond to 2 to 4 puffs every 3 to 4 hours; moderate exacerbations will require 6 to 10 puffs every 1 or 2 hours. Treatment should also be titrated depending upon the individual patient's response, and if there is a lack of response or other concern about how the patient is responding, the patient should be referred to an acute care facility. No additional medication is necessary if the rapid-acting inhaled β2-agonist produces a complete response (PEF returns to greater than 80 % of predicted or personal best) and the response lasts for 3 to 4 hours.

Glucocorticosteroids. Oral glucocorticosteroids (0.5 to 1 mg of prednisolone/kg or equivalent during a 24-hour period) should be used to treat exacerbations, especially if they develop after instituting the other short-term treatment options recommended for loss of control. If patients fail to respond to bronchodilator therapy, as indicated by persistent airflow obstruction, prompt transfer to an acute care setting is recommended, especially if they are in a high risk group.

8. PNEUMONIA

PNEUMONIA is acute inflammation of the lungs caused by infection. Initial diagnosis is usually based on chest x-ray.

Classification

In the clinical situation, **anatomical** (radiographical) appearance (e.g. lobar pneumonia or bronchopneumonia) gives little practical information about cause. Likewise, **microbiological classification** of pneumonia is not practical as causative organisms may not be identifie or diagnosis takes several days. Specific pathogens causing pneumonia cannot be found in < 50 % of patients, even with extensive diagnostic investigation. But because pathogens and outcomes tend to be similar by setting and host risk factors, pneumonias can be categorized as

• **Community-acquired pneumunia:** describes infection occurring within 48 hours of hospital admission in patients who have not been hospitalized for more than 14 days. The most frequently identifie organism is *Streptococcus pneumonia* (20–75 %). *Mycoplasma pneumonia, Chlamidia pneumonia* and *Legionella spp.,* the «atypical» bacterial patogens (2–25 %) and viral infections (8–12 %) are relatively common causes. *Haemophilus influenza* and *Moraxella catarrhalis* are associated with COPD exacerbations, and staphylococcal infection may follow influenza. Alcoholic, diabetic and nursing home patients are prone to staphylococcal, anaerobic and Gram-negative organisms.

• **Hospital-acquired (nosocomial) pneumonia** (including ventilator-acquired and postoperative): any infections developing more than 2 days after hospital admission. Likely organisms are Gram-negative bacilli (~70 %) or staphylococcus (~15 %).

• **Aspiration pneumonia:** bacteroides and other anaerobic infections follow aspiration of oropharingeal contens.

• **Pneumonia occurring in immunocompromised people:** immunosuppressed patients (e.g. steroids, chemotherapy and HIV) are susceptible to viral, fungal and mycobacterial infections.

These categorizations allow treatment to be selected empirically.

Epidemiology

Annual incidence: 5–11 cases per 1000 adult population; 15–45 % require hospitalization (1–4 cases per 1000) of whom 5–10 % are treated in ICU. Incidence is highest in the very young and elderly. Mortality: 5–12 % in hospitalized patients; 25-50% in ICU patients. Seasonal variation: with peaks (e.g. *Mycoplasma* in autumn, *Staphylococcus* in spring) and annual cycles occur (e.g. 4-yearly *Mycoplasma* epidemics). Frequent viral infections increase pneumonia in winter.

Risk factors

• Age: >65, <5 years old (e.g. *Mycoplasma* in young adults).

• Chronic disease (e.g. renal and lung).

• Diabetes mellitus.

• Immunosuppression (e.g. drugs and HIV).

• Alcohol dependency.

• Aspiration (e.g. epilepsy).

• Recent viral illness (e.g. influenza).

• Malnutrition.

• Mechanical ventilation.

• Postoperative (e.g. obesity and smoking).

• Environmental (e.g. psittacosis with pet birds and erlichiosis due to tick bites).

• Occupational (e.g. brucellosis in abattoir workers and Q fever in sheep workers).

• Travel abroad (e.g. paragonimiasis and coccidiomycosis in southwest USA).

• Air conditioning (e.g. *Legionella*).

PATHOGENESIS

The airways and lungs are constantly exposed to pathogens in the external environment; the upper airways and oropharynx in particular are colonized with so-called normal flora rendered harmless by host defenses. Infection develops when pathogens that are inhaled or aspirated or reach the lungs via the bloodstream or contiguous spread overcome multiple host defenses.

Upper airway defenses include salivary IgA, proteases, and lysozymes; growth inhibitors produced by normal flora; and fibronectin, which coats the mucosa and inhibits adherence. Nonspecific lower airway defenses include cough, mucociliary clearance, and airway angulation preventing infection in airspaces. Specific lower airway defenses include various pathogen-specific immune mechanisms, including IgA and IgG opsonization, anti-inflammatory effects of surfactant, phagocytosis by alveolar macrophages, and T-cell–mediated immune responses. These mechanisms protect most people against infection. But numerous conditions alter normal flora (eg, systemic illness, undernutrition, hospital or nursing home exposure, antibiotic exposure) or impair these defenses (eg, cigarette smoking, nasogastric or endotracheal intubation). Pathogens that then reach airspaces can multiply and cause pneumonia.

The pathologic process common to all pneumonias is infection and inflammation of the distal pulmonary parenchyma. An influx of polymorphonuclear leukocytes (PMNs), edema fluid, erythrocytes, mononuclear cells, and fibrin is seen to a variable extent in all cases. The bacterial pneumonias, in

particular, are characterized by an exuberant outpouring of PMNs into alveolar spaces as they attempt to limit proliferation of the invading bacteria.

In some cases of pneumonia, the organisms are not highly destructive to lung tissue, even though an exuberant inflammatory process may be seen. Pneumococcal pneumonia classically (although not always) behaves in this way, and the healing process is associated with restoration of relatively normal parenchymal architecture. In other cases, when the organisms are more destructive, tissue necrosis may occur, with resulting cavity formation or scarring of the parenchyma. Many cases of staphylococcal and anaerobic pneumonias follow this more destructive course.

CLINICAL FEATURES

In many ways the clinical manifestations of pneumonia are similar, even when different infectious agents are involved. In many cases, a specific agent cannot be clearly identified, and patients often are managed in an empiric way based on the setting in which they present.

The most important constellation of symptoms in almost any type of pneumonia consists of fever, cough, and, often, shortness of breath. The cough is nonproductive in some cases, particularly in those pneumonias caused by viruses or mycoplasma; in others, especially bacterial pneumonias, sputum production is a prominent feature. When the inflammatory process in the pulmonary parenchyma extends out to the pleural surface, the patient often reports pleuritic chest pain. If the fever is high and «spiking», patients frequently experience shaking chills associated with the rapid rise in body temperature.

Physical examination. Patients often have tachycardia, tachypnea, and fever. Examination of the chest typically reveals crackles or rales overlying the region of the pneumonia. If dense consolidation is present and the bronchus supplying the area is patent, then sound transmission is greatly increased through the consolidated, pneumonic area. As a result, breath sounds may be bronchial in quality, fremitus is increased, and egophony is present. The consolidated area is characteristically dull to percussion of the overlying chest wall.

Examination of the ***peripheral blood*** generally shows an increase in the white blood count (leukocytosis). Especially in patients with bacterial pneumonia, the leukocytosis is composed primarily of PMNs, and a shift toward immature, younger neutrophils (i.e., bands) may be seen.

In pneumococcal pneumonia, the onset of the clinical illness often is relatively abrupt, with shaking chills and high fever. Cough may be productive of yellow, green, or blood-tinged (rusty-colored) sputum. Before the development of pneumonia, patients often experience a viral upper respiratory tract infection, which presumably is an important predisposing feature.

Mycoplasmal pneumonia, in contrast to pneumococcal pneumonia, characteristically has a somewhat slower, more insidious onset. Cough is a particularly prominent symptom, but it often is nonproductive. Fever is not as high, and shaking chills are uncommon. Young adults are the individuals most likely to have mycoplasmal pneumonia, although the disease is not limited to this age group.

Patients with either staphylococcal or gram-negative bacillary pneumonias are often quite ill. Frequently, these patients have complex underlying medical problems and have already been hospitalized. Many have impaired defense mechanisms or have recently received antibiotics. Staphylococcal pneumonia may be seen as a secondary complication of influenza infection or as a result of dissemination of the organism through the bloodstream.

Pneumonia with anaerobic organisms generally occurs in patients with impaired consciousness or difficulty swallowing who cannot adequately protect the airway from aspiration of oropharyngeal secretions. Dentition often is poor, and patients frequently have gingivitis or periodontal abscesses. Clinical onset of the pneumonia tends to be gradual, and sputum may have a foul odor, suggesting anaerobic infection.

Because the organisms are likely to cause substantial tissue destruction, necrosis of affected tissue and abscess formation are relatively common sequelae.

Pneumonia caused by *L. pneumophila,* commonly called legionnaires' disease, can be seen as isolated cases or localized outbreaks. Otherwise healthy hosts may be affected, but patients with impaired respiratory defense mechanisms appear to be predisposed. Patients often are extremely ill, not only with respiratory compromise and even respiratory failure but also with nonrespiratory manifestations; specifically, gastrointestinal, central nervous system, hepatic, and renal abnormalities may accompany the pneumonia.

DIAGNOSTIC APPROACH

Chest X-ray. The single most useful tool for assessing pneumonia at the macroscopic level is the chest radiograph. The radiograph not only confirms the presence of a pneumonia; it also shows the distribution and extent of disease and sometimes gives clues about the nature of the etiologic agent. The classic pattern for *S. pneumoniae* (pneumococcus) and *K. pneumonia* is a lobar pneumonia. Staphylococcal and many of the gram-negative pneumonias may be localized or extensive and often follow a patchy distribution. *Mycoplasma* organisms can produce a variety of radiographic presentations, classically described as being more impressive than the clinical picture would suggest. Pneumonias caused by aspiration of oropharyngeal secretions characteristically involve the dependent regions

of lung: the lower lobe in the upright patient or the posterior segment of the upper lobe or superior segment of the lower lobe in the supine patient.

The chest radiograph is useful for demonstrating pleural fluid, which frequently accompanies pneumonia, particularly of bacterial origin. The pleural fluid can be either thin and serous or thick and purulent; in the latter case the term *empyema* is used.

Microscopic examination of the sputum may play an important role in the evaluation of patients with pneumonia. In a good sputum specimen (i.e., one that contains few squamous epithelial cells picked up in transit through the upper respiratory tract), inflammatory cells and bacteria can be seen.

In most bacterial pneumonias, large numbers of PMNs are seen in the sputum. In contrast, mycoplasmal and viral pneumonias have fewer PMNs and more mononuclear inflammatory cells. Pneumococcal, staphylococcal, and gram-negative bacillary pneumonias commonly demonstrate a relatively homogeneous population of the infecting bacteria. Anaerobic aspiration pneumonias, caused by a mixture of organisms from the oropharynx, show a mixed population of bacteria of many different morphologies. In legionnaires' disease, the bacterium does not stain well with the usual Gram stain reagent and therefore is not seen with conventional staining techniques. In mycoplasmal and viral pneumonia, the infecting agent is not visualized by light microscopy, and only the predominantly mononuclear cell inflammatory response is seen.

In conjunction with the initial Gram stain and microscopic examination of sputum, the specimen is cultured for bacteria. However, some bacteria are relatively difficult to grow, and in many, if not most, cases the initial Gram stain is just as important in making the etiologic diagnosis. Special culture media are available to facilitate the growth of *Legionella* species.

When sputum is not spontaneously expectorated by the patient, other methods for obtaining respiratory secretions (or even material directly from the lung parenchyma) may be necessary. The techniques that have been used, including flexible bronchoscopy, needle aspiration of the lung, and occasionally surgical lung biopsy.

Routine stains and cultures of sputum are not useful for three of the important causes of pneumonia: *Mycoplasma*, *Chlamydophila*, and *Legionella*.

Sometimes the diagnosis can be confirmed by a variety of serologic techniques that demonstrate a rise in antibody titer against the organism, but these techniques provide a retrospective diagnosis and are not useful clinically. Polymerase chain reaction methods are being investigated for all three organisms and may have an important role in the future. The functional assessment of patients with acute infectious pneumonia usually is limited to evaluation of gas exchange. Arterial blood gas values characteristically demonstrate hypoxemia, accompanied by a normal or decreased P_{CO_2}. Pulmonary function tests have little usefulness in this setting.

TREATMENT

Severity and Admission to Hospital

When a diagnosis of pneumonia is suspected, one of the important first steps is to evaluate severity and determine whether the patient needs hospital care.

Hospitalization is required for the development of severe pneumonia or the inability to perform adequate care of all medical prescriptions in the home.

Severity assessment

Severity scoring (CRB-65 and CURB-65 scores) to stratify patients into mortality groups suitable for different management pathways.

Table 8.1 — Non-hospital (i.e. community) management of CAP using the recently validated CRB-65 score
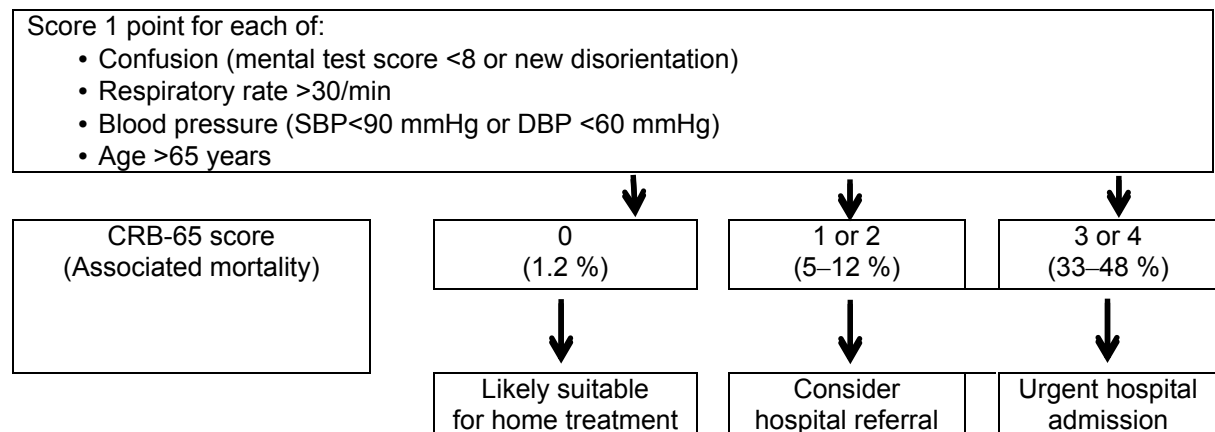
Score 1 point for each of:
• Confusion (mental test score <8 or new disorientation)
• Respiratory rate >30/min
• Blood pressure (SBP<90 mmHg or DBP <60 mmHg)
• Age >65 years

CRB-65 score (Associated mortality)	0 (1.2 %)	1 or 2 (5–12 %)	3 or 4 (33–48 %)
	Likely suitable for home treatment	Consider hospital referral	Urgent hospital admission

Table 8.2 — Management of CAP in patients admitted to hospital using the recently validated CURB-65 score

Score 1 point for each of:
• Confusion (mental test score <8 or new disorientation)
• Urea >7 mmol/L (i.e. includes use of laboratory tests)
• Respiratory rate > 30/min
• Blood pressure (SBP<90 mmHg or DBP <60 mmHg)
• Age >65 years

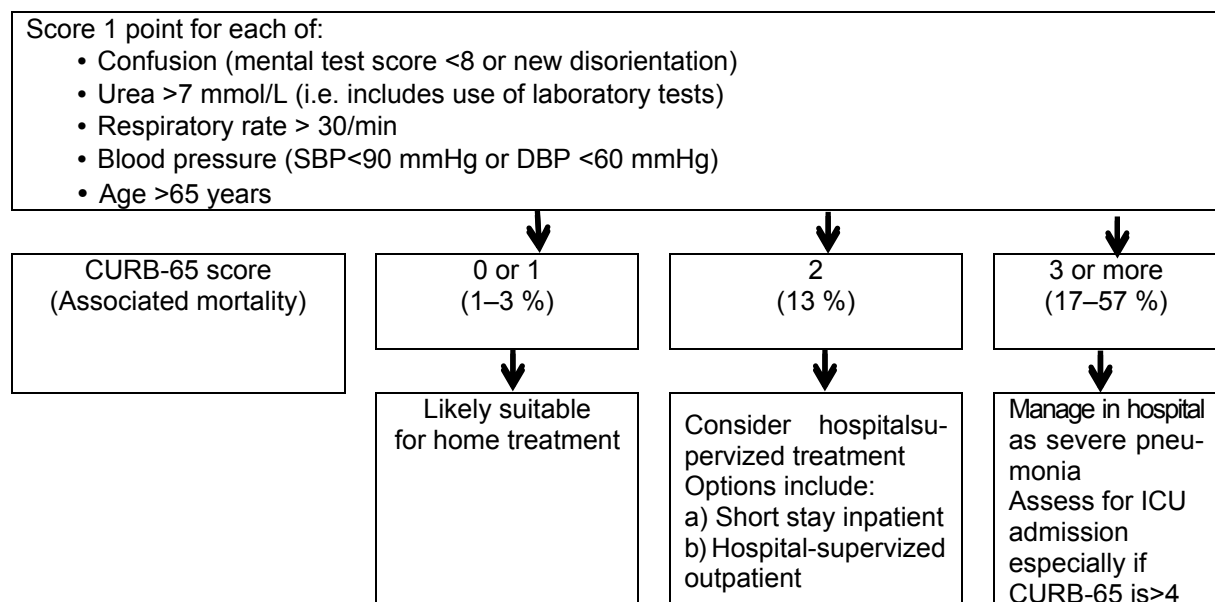| CURB-65 score (Associated mortality)	0 or 1 (1–3 %)	2 (13 %)	3 or more (17–57 %)
	Likely suitable for home treatment	Consider hospitalsupervized treatment Options include: a) Short stay inpatient b) Hospital-supervized outpatient	Manage in hospital as severe pneumonia Assess for ICU admission especially if CURB-65 is>4

Table 8.3 — Criteria severe of CAP

Clinical and instrumental	Laboratory
Acute respiratory failure: Respiratory rate > 30 min, SaO$_2$ <90 Hypotension: systolic blood pressure <90 mm Hg diastolic blood pressure < 60 mm Hg The defeat of two or more lobes Extrapulmonary site of infection (meningitis, pericarditis, etc.) Anuria	Leukopenia (<4 x 10^9/ L) Hypoxemia: PaO2 <60 mm Hg Hemoglobin <100 g / L Hematocrit <30 % Acute renal failure (creatinine levels > 176.7 mmol / L, urea > 7.0 mmol / L)

The question of preference for hospital treatment of pneumonia may be considered in the following cases:
• Age over 60 years.
• The presence of concomitant diseases (chronic bronchitis, COPD, bronchiectasis, cancer, diabetes, chronic renal failure, congestive heart failure, chronic alcoholism, drug abuse, expressed underweight, cerebrovascular disease).
• Ineffective starting antibiotic therapy.
• Pregnancy.
• Desire to the patient and / or family members.

Empirical antibiotic therapy
The initial antibiotic choice for CAP is empirical for the following reasons:
• In at least half the cases, responsible organisms will not be isolated by use of even the most sophisticated methods.
• Antibiotic treatment should be started as early as possible, without waiting for microbiologic results (if such investigations are performed). Delaying treatment increases the risk of complications and mortality, whereas correctly chosen empirical therapy improves outcome.
Recommendations for empiric therapy are presented in Table 8.4 (non-hospitalized patients).
The recommended duration of antibiotic treatment for CAP is 1 week when the infection is due to extracellular organisms and 2 weeks when it is thought to be due to intracellular infection.

Table 8.4 — Antibiotic therapy of pneumonia in non-hospitalized patients

Groups of patients	Most common pathogens	Antibiotics
Patients with no risk factors who do not require hospitalization, who have not used antibiotics in the previous 3 months	*S. pneumoniae, M. pneumoniae, C. pneumoniae, H. influenzae*	Aminopenicillin (amoxicillin) or newer (advanced-generation) macrolide
Patients with risk factors, who use of antibiotics within the prior 3 months	*S. pneumoniae, H. influenzae, C. pneumoniae, S. aureus, Aerobic gram-negative bacilli*	Aminopenicillin and penicillinase inhibitor (amoxiclav, unasyn) ± macrolide (azitromycin, clarithromycin) or fluoroquinolone (levofloxacin, moxifloxacin)

Evaluating the effectiveness of therapy is conducted within 48-72 hours. The main performance criteria: temperature reduction, reducing the symptoms of intoxication, dyspnea, respiratory failure. If no effect is necessary to reconsider the tactics of therapy and to evaluate the feasibility of hospitalization.

Table 8.5 — The choice of antibiotic with inefficiency starting regimen in non-hospitalized patients

Antibiotics for the treatment of stage 1	Antibiotics for the treatment of stage 2
Amoxicillin	Macrolide
Amoxicillin + clavulanic acid or Amoxicillin + sulbactam	Fluoroquinolone macrolide
Macrolide	Amoxicillin Amoxicillin + clavulanic acid or Amoxicillin + sulbactam Fluoroquinolone

The мain criterion for abolition of antibiotic is the resistant normalization of temperature for 48–72 hours and the positive dynamics of other symptoms:
• The temperature < 37,8.
• The heart rate < 100/min.
• Respiratory rate < 24 per minute.
• Systolic blood pressure> 90 mm Hg.

Radiographic manifestations resolved slowly than clinical chahges of pneumonia, and control chest X-ray can not be a criterion for determining antibiotic convincingly.

Table 8.6 — Antibiotic therapy of pneumonia in hospitalized patients

Groups of patients	Most common pathogens	Antibiotics
Non-severe pneumonia	*S. pneumoniae,* *S. aureus,* *C. pneumoniae,* *H. influenza,* *Enterobacteriaceae*	Amoxicillin/clavulanic acid ± macrolide Amoxicillin/sulbactam ± macrolide
Severe pneumonia	*S. pneumoniae,* *S. aureus,* *Legionella spp.,* *Enterobacteriaceae*	Aminopenicillin and penicillinase inhibitor (amoxiclav, unasyn) ± macrolide (azitromycin, clarithromycin) or fluoroquinolone (levofloxacin, moxifloxacin)

9. LUNG ABSCESS

Lung abscess is a necrotizing lung infection characterized by a pus-filled cavitary lesion.

Etiology

Most lung abscesses develop after aspiration of oral secretions by patients with gingivitis or poor oral hygiene. Typically, patients have altered consciousness as a result of alcohol intoxication, illicit drugs, anesthesia, sedatives, or opioids. Older patients and those unable to handle their oral secretions, often because of neurologic disease, are also at risk.

A less common cause of lung abscess is necrotizing pneumonia that may develop from hematogenous seeding of the lungs due to suppurative thromboembolism (eg, septic embolism due to IV drug use) or right-sided endocarditis. In contrast to aspiration, these conditions typically cause multiple rather than isolated lung abscesses.

The most common pathogens of lung abscesses due to aspiration are anaerobic bacteria, but about half of all cases involve both anaerobic and aerobic organisms. The most common aerobic pathogens are streptococci and staphylococci — sometimes methicillin-resistant *Staphylococcus aureus* (MRSA). An unusual but very important acute and often lethal form of lung necrosis is caused by *S. aureus* with genes for Panton-Valentine leukocidin. Very serious and fulminant cases may be caused by MRSA, which has become a rare but very important cause of necrotizing pneumonia in young previously healthy adults and children. Occasionally, cases are due to gram-negative bacteria, especially *Klebsiella*. Immunocompromised patients with lung abscess may have infection with *Nocardia*, *Mycobacteria* sp, or fungi. Some people, especially those from developing countries, are at risk of abscess due to *Mycobacterium tuberculosis*, and rare cases are due to amebic infection (eg, with *Entamoeba histolytica*), paragonimiasis, or *Burkholderia pseudomallei*.

Introduction of these pathogens into the lungs first causes inflammation, which leads to tissue necrosis and then abscess formation. The abscess usually ruptures into a bronchus, and its contents are expectorated, leaving an air- and fluid-filled cavity. In about one third of cases, direct or indirect extension (via bronchopleural fistula) into the pleural cavity results in empyema.

Symptoms and Signs

Symptoms of abscess due to anaerobic bacteria or mixed anaerobic and aerobic bacteria are usually chronic (eg, over weeks or months) and include productive cough, fever, sweats, and weight loss. Severe prostration may occur. Sputum may be purulent or blood-streaked and classically smells or tastes foul. Symptoms of abscess due to aerobic bacteria develop more

acutely and resemble bacterial pneumonia. Abscesses due to organisms other than anaerobes (eg, *Mycobacteria, Nocardia*) lack putrid respiratory secretions and may be more likely to occur in nondependent lung regions.

Signs of lung abscess, when present, are nonspecific and resemble those of pneumonia: decreased breath sounds indicating consolidation or effusion, temperature ≥ 38 C, crackles over the affected area, egophony, and dullness to percussion in the presence of effusion. Patients typically have signs of periodontal disease and a history of a predisposing cause of aspiration, such as dysphagia or a condition causing impaired consciousness.

Table 9.1 — Infectious Causes of Cavitary Lung Lesions

Causes	Examples (Disorder)
Aerobic organisms	*Burkholderia pseudomallei** *Klebsiella pneumonia** *Nocardia* sp[†] *Pseudomonas aeruginosa** *Staphylococcus aureus*[‡] *Streptococcus milleri*[‡] Other streptococci[‡]
Anaerobic organisms	*Actinomyces* sp[†] *Bacteroides* sp* *Clostridium* sp[†] *Fusobacterium* sp* *Peptostreptococcus* sp[‡] *Prevotella* sp*
Fungi	*Aspergillus* sp (aspergillosis) *Blastomyces dermatitidis* (blastomycosis) *Coccidioides immitis* (coccidioidomycosis) *Cryptococcus neoformans* (cryptococcosis) *Histoplasma capsulatum* (histoplasmosis) *Pneumocystis jirovecii* *Rhizomucor* (mucormycosis) *Rhizopus* sp (mucormycosis) *Sporothrix schenckii* (sporotrichosis)
Mycobacteria	*Mycobacterium avium-cellulare* *Mycobacterium kansasii* *Mycobacterium tuberculosis*
Parasites	*Entamoeba histolytica* (amebiasis) *Echinococcus granulosus* (echinococcosis) *Echinococcus multilocularis* (echinococcosis) *Paragonimus westermani* (paragonimiasis)

*Gram-negative bacilli.
[†]Gram-positive bacilli.
[‡]Gram-positive cocci.

Diagnosis:
- Chest x-ray.
- CT as needed.
- Sputum cultures (unless anaerobic infection is very likely), including for fungi and mycobacteria.
- Bronchoscopy as needed to exclude cancer.

Lung abscess is suspected based on history in a patient who is aspiration-prone due to altered consciousness or dysphagia and is confirmed by chest x-ray. In an anaerobic infection due to aspiration, chest x-ray classically shows consolidation with a single cavity containing an air-fluid level in portions of the lung that would be dependent when the patient is recumbent (eg, the posterior segments of the upper lobes or the superior or lateral basal segments of the lower lobes). This pattern helps distinguish anaerobic abscess from other causes of cavitary pulmonary disease, because diffuse or embolic pulmonary disease often causes multiple cavitations, and TB typically involves the apices.

CT is not routinely needed but may be useful when the x-ray suggests a cavitating lesion or when an underlying pulmonary mass obstructing the drainage of a lung segment is suspected.

Bronchial carcinoma can lead to obstruction that causes pneumonia and abscess formation. This should be suspected in smokers, recent smokers, and patients with unexplained cavitary lesions and no fever. Bronchoscopy is sometimes done to exclude cancer or the presence of a foreign body or to detect unusual pathogens, such as fungi.

Cultures: Anaerobic bacteria are rarely identifiable on culture because uncontaminated specimens are difficult to obtain and because most laboratories do not culture anaerobes well or often. If sputum is putrid, then anaerobic infection is assumed to be the cause. However, if empyema is present, pleural fluid provides a good source for anaerobic culture.

When clinical findings make anaerobic infection less likely, aerobic, fungal, or mycobacterial infection should be suspected, and attempts should be made to identify a pathogen. Cultures of sputum, bronchoscopic aspirates, or both are helpful. MRSA is generally found in both the sputum and blood cultures.

Treatment

- IV antibiotics or, for less seriously affected patients, oral antibiotics
- Percutaneous drainage or surgery if empyema present or no response to antibiotics

Treatment is with antibiotics. Clindamycin 600 mg IV q 6 to 8 h is usually the drug of choice because it has excellent activity against streptococci and anaerobic organisms. The primary alternative is a combination β-lactam/β-lactamase inhibitor (eg, ampicillin/sulbactam 1 to 2 g IV q 6 h, ticarcillin/clavulanate 3 to 6 g IV q 6 h, piperacillin/tazobactam 3 g IV q 6 h). Metronidazole 500 mg q 8 h may be used but must be combined with penicillin 2 million units q 6 h IV. Less seriously ill patients may be given oral antibiotics such asclindamycin 300 mg po q 6 h or amoxicillin/clavulanate 875/125 mg po q 12 h. IV regimens can be converted to oral ones when the patient defervesces. For very serious infections involving MSRA, the best treatment is vancomycin or linezolid.

Optimal duration of treatment is unknown, but common practice is to treat until the chest x-ray shows complete resolution, which generally takes 3 to 6 wk or longer. In general, the larger the abscess, the longer it will take for x-rays to show resolution.

Most authorities do not recommend chest physical therapy and postural drainage because they may cause spillage of infection into other bronchi with extension of the infection or acute obstruction. If the patient is weak or paralyzed or has respiratory failure, tracheostomy and suctioning may be necessary. Rarely, bronchoscopic aspiration helps facilitate drainage. An accompanying empyema must be drained. Percutaneous or surgical drainage of lung abscesses is necessary in the roughly 10 % of patients in whom lesions do not respond to antibiotics. Resistance to antibiotic treatment is most common with large cavities and with infections that complicate obstructions.

When surgery is necessary, lobectomy is the most common procedure; segmental resection may suffice for small lesions (< 6 cm diameter cavity). Pneumonectomy may be necessary for multiple abscesses or for pulmonary gangrene unresponsive to drug therapy.

10. LUNG CANCER

Lung cancer is a public health problem of immense proportions. It has been a source of great frustration to individual physicians and to the medical professsion in general.

The term lung cancer is used to describe cancer that arises in the airways or pulmonary parenchyma. More people die in the USA and Europe from lung cancer than from breast, prostate and colon cancer combined. Lung cancer has a worse prognosis than other common cancers, with an overall 5-year survival of 13 %.

Risk factors for the development of carcinoma of the lung

• Cigarette smoking is the single most important risk factor. The duration of the smoking history, the number of cigarettes smoked each day, the depth of inhalation, and the amount of each cigarette smoked all correlate with the risk for development of lung cancer. After quitting cigarettes, risk gradually declines over 15 years, but remains 2-5 times greater than in non-smokers. Passive smoking in non-smokers may increase the risk by approximately 1,5 %.

• OCCUPATIONAL FACTORS.

Asbestos exposure is the most common occupational risk. Shipbuilders, construction workers, and those who work with insulation and brake linings are among those who may be exposed to asbestos. The tumor generally becomes apparent more than 2 decades after exposure. The risk of lung cancer is markedly increased by the combined risk factors of asbestos exposure and smoking.

Other occupational factors are exposure to arsenic (in workers making pesticides, glass, pigments, and paints), ionizing radiation (especially in uranium miners), halo ethers (bis-chloromethyl ether and chloromethyl methyl ether in chemical industry workers), and polycyclic aromatic hydrocarbons (in petroleum, coal tar, and foundry workers).

• Radon exposure is perhaps the greatest element of lung cancer risk for neversmokers who have not been exposed to asbestos. Radon is a decay product of naturally occurring radium, which, in turn, is a breakdown product of uranium. Exposure to this carcinogen may occur indoors in homes built on soil that has a high radium content and is releasing radon into the surrounding environment.

• GENETIC FACTORS An inherited susceptibility for lung cancer has recently been established. A family history of lung cancer is recognized as predicting approximately a twofold increased risk after controlling for smoking, but a lung cancer gene per se has not yet been identified.

• PARENCHYMAL SCARRING Scar tissue within the lung can be a locus for the subsequent occurrence of lung cancer, called a scar carcinoma. The scarring may be either localized (e.g., resulting from an old focus of tuberculosis or another infection) or diffuse (e.g., from pulmonary fibrosis, whether idiopathic or associated with a specific cause).

Classification

Lung cancer is classified into primarily two subgroups: small-cell lung cancer (SCLC, 20–30 %) and nonsmall-cell lung cancer (NSCLC, 70–80 %). The distinction in subgroups is essential with regard to treatment and prognosis.

• Small cell lung cancer (SCLC) is highly aggressive and almost always occurs in smokers. SCLC arise from neuroendocrine cells in the bronchial submucosa, and typically present as a central mass with lymph node enlargement. It is rapidly growing, and roughly 60 % of patients have widespread metastatic disease at the time of diagnosis.

• Non-small cell lung cancer (NSCLC). The clinical behavior of NSCLC is more variable and depends on histologic type, but about 40% of patients have metastatic disease outside of the chest at the time of diagnosis. NSCLC types:

  ○ Adenocarcinoma (33 %) typically present as a peripheral nodule (<3 cm) or mass (>3 cm); it is the most common type in non-smokers, and mainly arise in areas of pulmonary scarring.

  ○ Squamous cell carcinoma (30 %) arise from bronchial epithelium, and generally present as a central mass with tumor visible in the airway, often with symptoms due to local tumor invasion (cough, haemoptysis, chest pain and hoarsness).

  ○ Large cell carcinoma (15 %) is undifferentiated, and lacks histological features of adenocarcinoma or squamous cell carcinoma. It generally presents as a large peripheral mass, often metastases.

Symptoms and Signs

About 25 % of lung cancers are asymptomatic and are detected incidentally with chest imaging. Symptoms and signs can result from local tumor progression, regional spread, or distant metastases. Paraneoplastic syndromes and constitutional symptoms may occur at any stage of the disease.

Local tumor: The local tumor can cause cough and, less commonly, dyspnea due to airway obstruction, postobstructive atelectasis, and lymphangitic spread. Fever may occur with postobstructive pneumonia. Up to half of patients report vague or localized chest pain. Hemoptysis is less common, and blood loss is minimal.

Regional spread: Regional spread of the tumor may cause pleuritic chest pain or dyspnea due to development of a pleural effusion, hoarse-

ness due to tumor encroachment on the recurrent laryngeal nerve, and dyspnea and hypoxia caused by diaphragmatic paralysis due to involvement of the phrenic nerve.

Superior vena cava (SVC) syndrome results from compression or invasion of the SVC and can cause headache or a sensation of head fullness, facial or upper-extremity swelling, supine breathlessness, and flushing (plethora). Physical signs of SVC syndrome include facial and upper-extremity edema, dilated neck and subcutaneous veins in the face and upper trunk, and facial and truncal plethora.

Apical tumors, usually NSCLC, can invade the brachial plexus, pleura, or ribs, causing shoulder and upper-extremity pain and weakness or atrophy of the ipsilateral hand (Pancoast's tumor). Horner's syndrome (ptosis, miosis, enophthalmos, and anhidrosis) results when the paravertebral sympathetic chain or cervical stellate ganglion is involved. Spread of the tumor to the pericardium may be asymptomatic or lead to constrictive pericarditis or cardiac tamponade. Rarely, esophageal compression causes dysphagia.

Metastases: Metastases eventually cause symptoms that vary by location. Metastases to the liver cause pain, GI symptoms, and ultimately hepatic insufficiency. Metastases to the brain cause behavioral changes, confusion, aphasia, seizures, paresis or paralysis, nausea and vomiting, and ultimately coma and death. Bone metastases can lead to severe pain and pathologic fractures. Although lung cancer commonly metastasizes to the adrenal glands, it rarely leads to adrenal insufficiency.

Paraneoplastic syndromes: Paraneoplastic syndromes are symptoms that occur at sites distant from a tumor or its metastases. Common paraneoplastic syndromes in patients with lung cancer include hypercalcemia (the tumor produces parathyroid hormone-related protein), syndrome of inappropriate antidiuretic hormone secretion (SIADH), finger clubbing with or without hypertrophic pulmonary osteoarthropathy, hypercoagulability with migratory superficial thrombophlebitis (Trousseau's syndrome), myasthenia (Eaton-Lambert syndrome), and various neurologic syndromes, including neuropathies, encephalopathies, encephalitides, myelopathies, and cerebellar disease. Mechanisms for neuromuscular syndromes involve tumor expression of autoantigens with production of autoantibodies, but the cause of most other syndromes is unknown.

Diagnosis
- Chest x-ray.
- CT.
- Cytopathology examination of pleural fluid or sputum.
- Usually bronchoscopy-guided biopsy and fine-needle aspiration.
- Sometimes open lung biopsy.

Chest x-ray is often the initial imaging test. It may show clearly defined abnormalities, such as a single mass or multifocal masses or a solitary pulmonary nodule, an enlarged hilum, widened mediastinum, tracheobronchial narrowing, atelectasis, nonresolving parenchymal infiltrates, cavitary lesions, or unexplained pleural thickening or effusion. These findings are suggestive but not diagnostic of lung cancer and require follow-up with CT and cytopathologic confirmation.

CT demonstrates many characteristic anatomic patterns and appearances that may confirm the diagnosis. CT also can guide needle biopsy of accessible lesions and is useful for staging.

The method used to obtain cells or tissue for confirmation depends on the accessibility of tissue and the location of lesions. Sputum or pleural fluid cytology is the least invasive method. In patients with productive cough, sputum specimens obtained on awakening may contain high concentrations of malignant cells, but yield for this method is < 50 % overall. Pleural fluid is another convenient source of cells; a malignant effusion is a poor prognostic sign. In general, false-negative cytology readings can be minimized by obtaining as large a volume of sputum or fluid as possible early in the day and sending the sample to the pathology laboratory immediately to minimize delays in processing, which lead to cell breakdown.

A percutaneous biopsy is the next least invasive procedure. It is more useful for metastatic sites (supraclavicular or other peripheral lymph nodes, pleura, liver, adrenals) than for lung lesions because of the 20 to 25 % risk of pneumothorax and the risk of false-negative results.

Bronchoscopy is the procedure most often used for diagnosing lung cancer. In theory, the procedure of choice for obtaining tissue is the one that is least invasive. In practice, bronchoscopy is often done in addition to or instead of less invasive procedures because diagnostic yields are greater and because bronchoscopy is important for staging. A combination of washings, brushings, biopsies, and fine-needle aspirations of visible endobronchial lesions and of paratracheal, subcarinal, mediastinal, and hilar lymph nodes often yields a tissue diagnosis.

Mediastinoscopy is the gold standard test for evaluating mediastinal lymph nodes but is a higher-risk procedure, which is usually used before surgery to confirm or exclude the presence of tumor in enlarged mediastinal lymph nodes.

Open lung biopsy, done via open thoracotomy or using video assistance, is indicated when less invasive methods do not provide a diagnosis in patients whose clinical characteristics and radiographic features strongly suggest that the tumor is resectable.

Screening: No screening studies are universally accepted for healthy patients who do not have lung cancer. Clinical trials have evalu-

ated screening chest x-rays in high-risk patients (smokers) to try to detect lung cancers at earlier stages, but mortality did not decline. Screening CT is being evaluated because it is more sensitive, but CT produces more false-positive results, which increase the number of unnecessary invasive diagnostic procedures needed to verify the CT findings. Such procedures are costly and risk additional complications. A strategy of yearly CT screening of smokers to evaluate indeterminate lesions is currently being studied. So far, this strategy does not seem to lessen mortality and cannot be recommended as routine practice. The future of screening may lie in a combination of molecular analysis for genetic markers (eg,*K-ras*, *p53*, *EGFR*), sputum cytometry, and detection of cancer-related volatile organic compounds (eg, alkane, benzene) in exhaled breath.

Staging

SCLC has 2 stages: limited and extensive. Limited-stage SCLC is cancer confined to one hemithorax (including ipsilateral lymph nodes) that can be encompassed within one tolerable radiation therapy port, unless there is a pleural or pericardial effusion. Extensive-stage disease is cancer outside a single hemithorax or the presence of malignant cells detected in pleural or pericardial effusions. Less than one third of patients with SCLC present with limited-stage disease; the remainder of patients often have extensive distant metastases.

NSCLC has 4 stages: I through IV. Staging is based on tumor size (T), tumor and lymph node location (N), and the presence or absence of distant metastases (M).

Prognosis

The overall prognosis for lung cancer is poor. The median survival time for limited-stage SCLC is 20 mo, with a 5-yr survival rate of 20 %. Patients with extensive-stage SCLC do especially poorly, with a 5-yr survival rate of < 1 %.

The 5-yr survival rate of patients with NSCLC varies by stage, from 60 to 70 % for patients with stage I disease to < 1% for patients with stage IV disease. On average, untreated patients with metastatic NSCLC survive 6 mo, whereas the median survival for treated patients is about 9 mo.

Treatment:

- Surgery (depending on cell type and stage).
- Chemotherapy.
- Radiation therapy.

Treatment in detail in the section of Oncology.

Table 10.1 — International Staging System for Lung Cancer (This staging system has been proposed by the International Association for the Study of Lung Cancer (IASLC)

Category	Description
Primary tumor (T)	
Tis	Carcinoma in situ
T1	Tumor ≤ 3 cm without invasion more proximal than the lobar bronchus
T2	Tumor > 3 cm but ≤ 7 cm *or* with any of the following: • Involves the main bronchus ≥ 2 cm distal to carina • Invades the visceral pleura • Associated with atelectasis or obstructive pneumonia that extends to the hilar region but does not involve the whole lung
T3	Tumor > 7 cm *or* with any of the following: • Invades the chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, or main bronchus < 2 cm distal to carina but not the carina • Atelectasis or obstructive pneumonitis of the entire lung • Separate tumor nodules in the same lobe
T4	Tumor of any size with either of the following: • Invades the mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina • ≥ 1 Satellite tumors in a different ipsilateral lobe
Regional lymph nodes (N)	
N0	No regional lymph node metastasis
N1	Metastasis to ipsilateral peribronchial or ipsilateral hilar lymph node or both and to intrapulmonary nodes, including that by direct extension of the primary tumor
N2	Metastasis to ipsilateral mediastinal or subcarinal lymph node or both
N3	Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node or a combination
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
Stage groupings	
Stage I: T1N0M0 or T2N0M0	Stage III: T1-T3N2M0 or T3N1M0 or T4N0-N1M0
Stage II: T1N1M0 or T2N1M0 or T3N0M0	Stage IV: T(any)N(any)M1

11. SARCOIDOSIS

Sarcoidosis is a disorder resulting in noncaseating granulomas in one or more organs and tissues; etiology is unknown. The lungs and lymphatic system are most often affected, but sarcoidosis may affect any organ.

Sarcoidosis affects mostly people aged 20 to 40 but occasionally affects children and older adults. Worldwide, prevalence is greatest in black Americans and northern Europeans, especially Scandinavians. Sarcoidosis is slightly more prevalent in women. The incidence increases in winter and early spring for unknown reasons.

Löfgren's syndrome: Löfgren's syndrome is a type of acute sarcoidosis that manifests as a triad of acute polyarthritis, erythema nodosum, and hilar adenopathy. It has distinct features, including fever, malaise, joint disease, and sometimes uveitis and parotitis. It is more common among Scandinavian and Irish women.

Löfgren's syndrome is often self-limited. Patients usually respond to NSAIDs. Rate of relapse is low.

Etiology

Sarcoidosis is thought to be due to an inflammatory response to environmental exposure in a genetically susceptible person. Proposed triggers include:
- Viral, bacterial, and mycobacterial infections.
- Inhalation of various agents: inorganic (eg, aluminum, zirconium, talc) or organic (eg, pine tree pollen, clay).

Pathophysiology

The unknown antigen triggers a cell-mediated immune response that is characterized by the accumulation of T lymphocytes and macrophages, release of cytokines and chemokines, and organization of responding cells into granulomas. Clusters of disease in families and communities suggest a genetic predisposition, shared exposures, or, less likely, person-to-person transmission.

The result of the inflammatory process is formation of noncaseating granulomas, the pathologic hallmark of sarcoidosis. Granulomas are collections of mononuclear cells and macrophages that are differentiated into epithelioid and multinucleated giant cells, surrounded by lymphocytes, plasma cells, mast cells, fibroblasts, and collagen. Granulomas occur most commonly in the lung and lymph nodes but can involve the liver, spleen, eyes, sinuses, skin, bones, joints, skeletal muscle, kidneys, reproductive organs, heart, salivary glands, and nervous system. Granulomas in the lungs are distributed along lymphatics, with most occurring in peribronchiolar, subpleural, and perilobular regions.

Symptoms and Signs

Symptoms and signs depend on the site and degree of involvement and vary over time, ranging from spontaneous remission to chronic indolent illness. Accordingly, frequent reassessment for new symptoms in different organs is needed. Most cases are probably asymptomatic and thus go undetected. Pulmonary disease occurs in > 90 % of adult patients.

Symptoms and signs may include dyspnea, cough, chest discomfort, and crackles. Fatigue, malaise, weakness, anorexia, weight loss, and low-grade fever are also common; sarcoidosis is an unusual cause of fever of unknown origin. Nontender lymphadenopathy is often the only sign. Systemic involvement causes various symptoms, which vary by race, sex, and age. Women are more likely to have erythema nodosum and eye or nervous system involvement. Men and older patients are more likely to be hypercalcemic.

In children < 4 yr, arthritis, rash, and uveitis are the most common manifestations. Sarcoidosis may be confused with juvenile RA in this age group.

Diagnosis:
- Chest imaging.
- Biopsy.
- Exclusion of other granulomatous disorders.

Sarcoidosis is most often suspected when hilar adenopathy is incidentally detected on chest x-ray. These changes are the most common abnormality, and the x-ray appearance is roughly predictive of the likelihood of spontaneous remission in patients with pulmonary involvement. Therefore, if sarcoidosis is suspected, a chest x-ray should be the first test if it has not already been done.

A normal chest x-ray generally excludes the diagnosis; however, high-resolution CT may be indicated if sarcoidosis is strongly suspected because CT is more sensitive for detecting hilar and mediastinal lymphadenopathy. CT findings in more advanced stages (II to IV) include thickening of the bronchovascular bundles and bronchial walls; beading of the interlobular septa; ground-glass opacification; parenchymal nodules, cysts, or cavities; and traction bronchiectasis.

When imaging suggests sarcoidosis, the diagnosis is confirmed by demonstration of noncaseating granulomas on biopsy and exclusion of alternative causes of granulomatous disease (see Table 3:Sarcoidosis: Differential Diagnosis of Sarcoidosis).

The diagnostic evaluation, therefore, requires the following:
- Selection of a biopsy site.
- Exclusion of other causes of granulomatous disease.
- Assessment of the severity and extent of disease to determine whether therapy is indicated.

Sites for biopsy: Appropriate biopsy sites may be obvious from physical examination and initial assessment; peripheral lymph nodes, skin lesions, and conjunctivae are all easily accessible. However, bronchoscopic transbronchial biopsy is the diagnostic procedure of choice in patients with intrathoracic involvement because sensitivity is as high as 90 % when an experienced clinician does the procedure. Video-assisted thoracoscopy can provide access to lung tissue when bronchoscopic transbronchial biopsy is nondiagnostic. Mediastinoscopy is sometimes done when hilar or mediastinal lymphadenopathy exists in the absence of pulmonary infiltrates, especially if lymphoma is in the differential diagnosis. However, even in patients with only mediastinal adenopathy on x-ray or CT, transbronchial biopsies are often diagnostic. Open lung biopsy provides another way to obtain tissue but requires general anesthesia and is now rarely necessary. Clinical and x-ray findings may be accurate enough for diagnosis in stage I disease or in stage II disease when biopsy is not possible.

Exclusion of other diagnoses: Exclusion of other diagnoses is critical, especially when symptoms and x-ray signs are minimal, because many other disorders and processes can cause granulomatous inflammation. Biopsy tissue should be cultured for fungi and mycobacteria. Exposure history to occupational (silicates, beryllium), environmental (moldy hay, birds, and other antigenic triggers of hypersensitivity pneumonitis), and infectious (TB, coccidioidomycosis, histoplasmosis) antigens should be explored. PPD skin testing should be done early in the assessment along with anergy controls.

Disease severity assessment: Severity is assessed with:
- Pulmonary function tests.
- Exercise pulse oximetry.

Pulmonary function test results are often normal in early stages but demonstrate restriction and reduced diffusing capacity for carbon monoxide (DLco) in advanced disease. Airflow obstruction also occurs and may suggest involvement of the bronchial mucosae. Pulse oximetry is often normal when measured at rest but may show effort desaturation with more extensive lung involvement. ABG analysis at rest and during exercise is more sensitive than pulse oximetry.

Recommended screening tests for extrapulmonary disease include:
- ECG.
- Slit-lamp ophthalmologic examination.
- Routine blood tests to evaluate renal and hepatic function.
- Serum Ca levels.

Echocardiography, neuroimaging, lumbar puncture, bone x-rays or MRI, and electromyography may be appropriate when symptoms suggest cardiac, neurologic, or rheumatologic disorders. Abdominal CT with

radiopaque dye is not routinely recommended but can provide evidence of hepatic or splenic involvement (eg, enlargement, hypolucent lesions).

Laboratory testing plays an adjunctive role in establishing the diagnosis and extent of organ involvement. CBC may show anemia, eosinophilia, or leukopenia. Serum Ca may be elevated because vitamin D analogs are produced by activated macrophages. BUN, creatinine, and liver function test results may be elevated in renal and hepatic sarcoidosis. Total protein may be elevated because of hypergammaglobulinemia. Elevated ESR is common but nonspecific. Measurement of Ca in a urine specimen collected over 24 h is recommended to exclude hypercalciuria, even in patients with normal serum Ca levels. Elevated serum ACE levels also suggest sarcoidosis but are nonspecific and may be low in patients taking ACE inhibitors or elevated in patients with various other conditions (eg, hyperthyroidism, Gaucher's disease, silicosis, mycobacterial disease, hypersensitivity pneumonitis). However, ACE levels may be useful for monitoring disease activity and therapeutic response in patients with confirmed sarcoidosis. Increased ACE levels in CSF may be useful for diagnosing CNS sarcoidosis.

Other adjunctive tests include bronchoalveolar lavage (BAL) and gallium scanning. BAL is used to help exclude other forms of interstitial lung disease if the diagnosis of sarcoidosis is in doubt and to rule out infection. The findings on BAL vary considerably, but lymphocytosis (lymphocytes >10 %), a CD4+/CD8+ ratio of > 3.5 in the lavage fluid cell differential, or both suggest the diagnosis in the proper clinical context. However, absence of these findings does not exclude sarcoidosis.

Whole-body gallium scanning may provide useful supportive evidence in the absence of tissue confirmation. Symmetric increased uptake in mediastinal and hilar nodes (lambda sign) and in lacrimal, parotid, and salivary glands (panda sign) are patterns highly suggestive of sarcoidosis. A negative result in patients taking prednisone is unreliable.

Prognosis

Although spontaneous improvement is common, the manifestations of the disorder and its severity are highly variable, and many patients require corticosteroids some time during the course of their disease. Thus, serial monitoring for evidence of relapse is imperative. In about 90 % of patients who have spontaneous remission, remission occurs within the first 2 yr after diagnosis; < 10 % of these patients have relapses after 2 yr. Patients who do not experience remission within 2 yr are likely to have chronic disease.

Sarcoidosis is thought to be chronic in up to 30 % of patients, and 10 to 20 % experience permanent sequelae. The disease is fatal in 1 to 5 % of patients, typically due to respiratory failure caused by pulmonary fibrosis, and less often due to pulmonary hemorrhage caused by asper-

gilloma. However, in Japan, infiltrative cardiomyopathy causing heart failure and arrhythmias is the most common cause of death.

Prognosis is worse for patients with extrapulmonary sarcoidosis and for blacks. Recovery occurs in 89 % of whites and 76 % of blacks with no extrathoracic disease and in 70 % of whites and 46 % of blacks with extrathoracic disease.

Good prognostic signs include:
- Erythema nodosum.
- Acute arthritis.

Poor prognostic signs include:
- Uveitis.
- Lupus pernio.
- Chronic hypercalcemia.
- Neurosarcoidosis.
- Nephrocalcinosis.
- Myocardial disease.
- Extensive pulmonary involvement.

Little difference is demonstrable in long-term outcome between treated and untreated patients, and relapse is common when treatment ends.

Treatment:
- Sometimes corticosteroids.
- Rarely immunosuppressants.

Because sarcoidosis often spontaneously resolves, asymptomatic patients and patients with mild symptoms do not require treatment, although they should be monitored for signs of deterioration. These patients can be followed with serial x-rays, pulmonary function tests (including diffusing capacity), and markers of extrathoracic involvement (eg, routine renal and liver function testing). Patients who require treatment regardless of stage include those with the following:
- Worsening symptoms.
- Limitation of activity.
- Markedly abnormal or deteriorating lung function.
- Worrisome x-ray changes (cavitation, fibrosis, conglomerate masses, signs of pulmonary hypertension).
- Heart, nervous system, or eye involvement.
- Renal or hepatic insufficiency or failure.
- Disfiguring skin or joint disease.

Treatment is with corticosteroids. A standard protocol is prednisone 0.3 to 1 mg/kg po once/day depending on symptoms and severity of findings. Alternate-day regimens are also used: eg, prednisone 40 to 60 mg po once every other day. Although patients rarely require > 40 mg/day, higher doses may be needed to reduce complications in patients with ocular, myocardial, or neurologic disease. Response usually occurs within 2 to 4 wk, so

symptoms and results of chest x-ray and pulmonary function tests may be reassessed between 4 and 12 wk. Chronic, insidious cases may respond more slowly. Corticosteroids are tapered to a maintenance dose (eg, prednisone ≤ 10 mg every other day if possible) after evidence of response and are continued for a minimum of 12 mo if improvement occurs. The optimal duration of treatment is unknown. Premature taper can result in relapse. The drug is slowly stopped if response is absent or equivocal. Corticosteroids can ultimately be stopped in most patients, but because relapse occurs up to 50 % of the time, monitoring should be repeated, usually every 3 to 6 mo. Corticosteroid treatment should be resumed for recurrence of symptoms and signs, including dyspnea, arthralgia, fever, hepatic insufficiency, cardiac arrhythmia, CNS involvement, hypercalcemia, ocular disease uncontrolled by local drugs, and disfiguring skin lesions.

Data on use of inhaled corticosteroids for pulmonary sarcoidosis are not definitive, but some evidence suggests that this route of administration can relieve cough in patients with endobronchial involvement. Topical corticosteroids may be useful in some cases of dermatologic and ocular disease.

About 10 % of patients requiring therapy are unresponsive to tolerable doses of a corticosteroid and should be given a 6-mo trial of methotrexate starting at 2.5 mg po once/wk and increasing in increments of 2.5 mg /wk to a total of 10 to 15 mg/wk as tolerated to keep the WBC count > 3000/μL. Initially,methotrexate and corticosteroids are both given; over 8 wk, the corticosteroid dose can be tapered and, in many cases, stopped. The maximal response to methotrexate, however, may take 6 to 12 mo. In such cases, prednisone must be tapered more slowly. Serial blood counts and liver enzyme tests should be done every 1 to 2 wk initially and then every 4 to 6 wk once a stable dose is achieved. Folate (1 mg po once/day) is recommended for patients treated with methotrexate.

Other drugs reported to be effective in small numbers of patients who are corticosteroid-resistant or who experience complicating adverse effects include azathioprine cyclophosphamide, chlorambucil, chloroquine or hydroxychloroquine, thalidomide, pentoxifylline, and infliximab.

Hydroxychloroquine 200 mg po bid to tid can be as effective as corticosteroids for treating hypercalcemia or disfiguring skin sarcoidosis. Although immunosuppressants are often more effective in refractory cases, relapse is common after cessation.

Lung transplantation is an option for patients with end-stage pulmonary involvement, although disease may recur in the transplanted organ.

12. PULMONARY EMBOLISM

Pulmonary embolism is one of the most important disorders that affect the pulmonary vasculature.

The term pulmonary embolism or, more precisely, pulmonary thromboembolism refers to movement of a blood clot from a systemic vein through the right side of the heart to the pulmonary circulation, where it lodges in one or more branches of the pulmonary artery. The clinical consequences of this common problem are quite variable, ranging from none to sudden death, depending on the size of the embolus and the underlying medical condition of the patient.

ETIOLOGY AND PATHOGENESIS

A thrombus, that is, a blood clot, is the material that travels to the pulmonary circulation in pulmonary thromboembolic disease. Other material also can travel via the vasculature to the pulmonary arteries, including tumor cells or fragments, fat, amniotic fluid, and a variety of foreign materials that can be introduced into the circulation.

In the majority of cases, the lower extremities are the source of thrombi that embolize to the lungs. Although these thrombi frequently originate in the veins of the calf, propagation of the clots to the veins of the thigh is necessary to produce sufficiently large thromboemboli that can obstruct major portions of the pulmonary vascular bed and become important clinically. Rarely do pulmonary emboli originate in the arms, pelvis, or right-sided chambers of the heart; combined, these sources probably account for less than 10 % of all pulmonary emboli. However, not all thrombi resulting in embolic disease are clinically apparent. In fact, only approximately 50 % of patients with pulmonary emboli have previous clinical evidence of venous thrombosis in the lower extremities or elsewhere.

The following three factors are commonly stated to potentially contribute to the genesis of venous thrombosis: (1) alteration in the mechanism of blood coagulation (i.e., hypercoagulability), (2) damage to the endothelium of the vessel wall, and (3) stasis or stagnation of blood flow. In practice, many specific risk factors for thromboemboli have been identified, including immobilization (e.g., bed rest, prolonged sitting during travel, immobilization of an extremity after fracture), the postoperative state, congestive heart failure, obesity, underlying carcinoma, pregnancy and the postpartum state, use of oral contraceptives, and chronic deep venous insufficiency. Patients at particularly high risk are those who had trauma or surgery related to the pelvis or lower extremities, especially hip fracture or hip or knee replacement.

A number of genetic predispositions to hypercoagulability are recognized. They include deficiency or abnormal function of proteins with anti-

thrombotic activity (e.g., antithrombin III, protein C, protein S) or the presence of abnormal variants of some of the clotting factors that are part of the coagulation cascade, especially factor V and prothrombin (factor II). In the genetic defect called factor V Leiden, which usually is due to a single base pair substitution leading to replacement of an arginine residue by glutamine, the factor V protein becomes resistant to the action of activated protein C.

In the genetic variant of prothrombin often called the prothrombin gene mutation, there is also a single base pair deletion that, by an unknown mechanism, leads to increased plasma levels of prothrombin and predisposes to venous thrombosis.

Table 12.1 — Risk factors for deep venous thrombosis and pulmonary embolism

Surgery	Hip, knee, gynaecological procedures
Trauma	Spinal trauma
General factors	Age, obesity, smoking, oral contraceptive pill (OCP)
Underlying disease	Malignancy, sepsis, stroke, autoimmune disease
Cardiovascular disease	Low flow states (e.g. cardiac failure and immobility) Vascular injury (e.g. atherosclerosis and catheters)
Inherited disorders (less common)	Deficiencies (e.g. antithrombin III, protein C and protein S) Clotting disorders (e.g. factor V leiden, antiphospholipid syndrome and dysfibrinogenaemias)

PATHOLOGY

When a thrombus embolizes to the lung, respiratory or circulatory abnormalities occur due to sudden occlusion of a pulmonary artery or arteriole. Occlusion of regional perfusion causes an increase in dead space, necessitating an increase in minute ventilation to maintain normal $P_a co_2$. Surfactant production distal to the embolus may be reduced after 24 hours, resulting in atelectasis. Hypoxaemia is common and mostly due to V_a/Q mismatch. Pulmonary infarction occurs in less than 25% of cases of PE. Circulatory complications arise from obliteration of the pulmonary vascular bed and a reduction of cardiac output. Severity is related to the amount of lung embolized and the pre-existing state of the pulmonary vasculature and right ventricle (RV). A single large embolus can be catastrophic, whereas multiple small emboli can cause pruning of smaller arteries. Circulatory collapse may occur with more than 50% obstruction of the pulmonary vascular bed. Less severe emboli may be fatal to patients with pre-exiting lung or heart disease.

CLINICAL FEATURES

Most frequently, pulmonary embolism develops in the setting of one of the risk factors previously mentioned. Commonly, the embolus does not produce any significant symptoms, and the entire episode goes un-

noticed by the patient and the physician. When the patient does have symptoms, acute onset of dyspnea is the most frequent complaint. Less common is pleuritic chest pain or hemoptysis. Syncope is an occasional presentation, particularly in the setting of a massive embolus, defined as the obstruction of two or more lobes (or an equivalent number of segments).

On physical examination, the most common findings are tachycardia and tachypnea. The chest examination may be entirely normal or may reveal a variety of nonspecific findings, such as decreased air entry, localized rales, or wheezing. With pulmonary infarction extending to the pleura, a pleural friction rub may be detected, as may findings of a pleural effusion. Cardiac examination may show evidence of acute right ventricular overload, that is, acute cor pulmonale, in which case the pulmonic component of the second heart sound (P2) is increased, a right-sided S4 is heard, and a right ventricular heave may be present. If the right ventricle fails, a right-sided S3 may be heard, and jugular veins may be distended. Examination of the lower extremities may reveal changes suggesting a thrombus, including tenderness, swelling, or a cord (palpable clot within a vessel). However, only a minority of patients with emboli arising from leg veins have clinical evidence of deep venous thrombosis, so the absence of these findings should not be surprising or overly reassuring.

DIAGNOSTIC EVALUATION

The initial diagnostic evaluation of the patient with suspected pulmonary embolism generally includes a chest radiograph and measurement of arterial blood gases. For patients in whom the diagnosis is considered less likely, the clinician may start with a d-dimer assay. D-dimer is a by-product of intrinsic fibrinolysis; thus, elevated levels occur in the presence of a recent thrombus. However, elevated levels are not specific for venous thrombus because many patients without DVT or PE also have elevated levels. More importantly, absence of elevated levels suggests the absence of recent thrombus because the test is sensitive; > 95 % of patients with DVT or PE have elevated levels. Thus, a low d-dimer level has a negative predictive value of > 95 %, making such a result sufficiently reliable for excluding the diagnosis of PE in routine practice among patients with a low or moderate pre-test probability.

The radiographic findings in acute pulmonary embolism are quite variable. Most frequently, the radiographic findings are normal. When they are not, the abnormalities often are nonspecific, including areas of atelectasis or elevation of a hemidiaphragm, indicating volume loss. The volume loss may be related to decreased ventilation to the involved area as a result of small airways constriction and possibly loss of surfactant. If pleuritic chest pain is present, the patient may try to prevent pain by breathing more shallowly, which contributes to atelectasis.

Occasionally, the chest radiograph reveals a localized area of decreased lung vascular markings corresponding to the region in which the vessel has been occluded. This finding is called Westermark's sign but often is difficult to read unless prior radiographs are available for comparison. With a large proximal embolus, occasionally enlargement of a pulmonary artery near the hilum occurs as a result of distention of the vessel by the clot itself. An apparent abrupt termination of the vessel may occur, although this usually is difficult to see on a plain chest radiograph.

Both congestive atelectasis and infarction may appear as an opacified region on the radiograph. Classically, the density is shaped like a truncated cone, fanning out toward and reaching the pleural surface. This finding, called a Hampton's hump, is relatively infrequent. Pleural effusions may be seen as an accompaniment of pulmonary embolic disease. Pleural effusions associated with pulmonary embolism may be either exudative or transudative and contain a variable number of red blood cells.

Chest x-ray can also help exclude pneumonia.

Pulse oximetry provides a quick way to assess oxygenation; hypoxemia is one sign of PE, and it requires further evaluation. ABG measurement may show an increased alveolar to arterial oxygen (A-a) gradient or hypocapnia; one or both of these tests are moderately sensitive for PE but are not specific. ABG testing should be considered particularly for patients with dyspnea or tachypnea who do not have hypoxemia detected with pulse oximetry.

ECG most often shows tachycardia and various ST-T wave abnormalities, which are not specific for PE. An S1Q3T3 or a new right bundle branch block may indicate the effect of abrupt rise in right ventricular pressure on right ventricular conduction; these findings are moderately specific but insensitive, occurring in only about 5 % of patients. Right axis deviation (R > S in V1) and P-pulmonale may be present. T-wave inversion in leads V1 to V4 also occurs.

V/Q scans detect areas of lung that are ventilated but not perfused, as occurs in PE; results are reported as low, intermediate, or high probability of PE based on patterns of V/Q mismatch. A completely normal scan excludes PE with nearly 100 % accuracy, but a low probability scan still carries a 15 % likelihood of PE. Perfusion deficits may occur in many other lung conditions, including pleural effusion, chest mass, pulmonary hypertension, pneumonia, and COPD. With an intermediate probability scan, there is a 30 to 40 % probability of PE; with a high probability scan, there is an 80 to 90 % probability of PE.

Duplex ultrasonography is a safe, noninvasive, portable technique for detecting lower extremity (primarily femoral vein) thrombi. A clot can be detected by visualizing the lining of the vein, by showing incompressibility of the vein, or by showing reduced flow by Doppler ultrasonography. The test has a sensitiv-

ity of > 90 % and a specificity of > 95 % for thrombus. It cannot reliably detect a clot in calf or iliac veins. Absence of thrombi in the femoral veins does not exclude the possibility of thrombus from other sources, but patients with negative results on Doppler duplex ultrasonography have > 95 % event-free survival, because thrombi from other sources are so much less common.

CT angiography is an alternative to V/Q scanning and pulmonary arteriography in most settings because it is fast, available, and noninvasive and gives more information about other lung pathology. However, patients must be able to hold their breath for several seconds. The sensitivity of CT angiography is highest for PE in lobar and segmental vessels and lowest for emboli in smaller subsegmental vessels (about 30% of all PEs) and thus is less sensitive than perfusion scans. In studies done using older scanners, overall sensitivities range from 53 to 100%; values are at the lower end of the range for subsegmental vessels. Specificities range from 81 to 100 %. A positive scan may be diagnostic of PE, but a negative scan does not necessarily exclude subsegmental disease, though the clinical significance of emboli in smaller subsegmental vessels remains to be determined. Newer multidetector scans are more sensitive (about 83 %) and are specific (about 96 %) overall. Magnetic resonance angiography (MRA) is an alternative to CT angiography for patients who cannot tolerate contrast agents and for pregnant patients

Echocardiography as a diagnostic test for PE is controversial. Its sensitivity is > 80 % for detecting right ventricular dysfunction (eg, dilation and hypokinesis, which occur when pulmonary artery pressure exceeds 40 mm Hg). Right ventricular dysfunction is a useful measure of hemodynamic severity in acute PE, but dysfunction is present in several disorders, including COPD, heart failure, and sleep apnea, and is therefore a nonspecific finding. Estimation of pulmonary artery systolic pressure using Doppler flow signals gives additional useful information about the severity of acute PE. Absence of right ventricular dysfunction or pulmonary hypertension makes the diagnosis of a large PE unlikely but does not exclude the diagnosis of a smaller one.

Cardiac marker testing is evolving as a useful means of stratifying mortality risk in patients with acute PE. Elevated troponin levels can signify right ventricular strain. Elevated brain natriuretic peptide (BNP) and pro-BNP levels are not helpful, but low levels appear to signify good prognosis. The clinical role of these tests remains to be determined, because they are not specific for right ventricular strain or for PE.

Prognosis
An estimated 10 % of patients with PE die within 1 h. Of those patients who survive the first hour, only about 30 % are diagnosed and receive treatment; > 95 % of these patients survive. Thus, most patients

with PE are never diagnosed; it is in such patients that most mortality from PE occurs. The best prospects for reducing mortality lie in improving diagnosis, not in improving treatment. Patients with chronic thromboembolic disease represent a tiny fraction of patients with PE who survive. Anticoagulant therapy reduces the rate of recurrence of PE to about 5 % in all patients.

TREATMENT

Initial treatment of PE is O2 for hypoxemia and IV 0.9% saline and vasopressors for hypotension and anticoagulation. All patients with strongly suspected or confirmed PE should be hospitalized and, ideally, should also be continually monitored for life-threatening cardiovascular complications in the first 24 to 48 h. Clot elimination should be considered in patients with massive PE at the time of diagnosis.

Standard treatment of a pulmonary embolus involves anticoagulant therapy, initially intravenous unfractionated heparin (UFH) or subcutaneous low-molecular-weight heparin (LMWH) for 5-7 days, and then an oral coumarin derivative (warfarin), the latter usually given for at least 3 to 6 months. UFH and warfarin must be monitored as subtherapeutic levels increase the risk of recurrent thromboembolism. LMWH is more bioavailable and does not require monitoring. Patients with inherited or acquired hypercoagulability may require lifelong therapy.

In patients with contraindication to anticoagulation (recent surgery, haemorrhagic stroke, central nervous system metastases, active bleeding) or recurrent PE while on therapeutic anticoagulation, an inferior vena cava filter may fatal PE.

Although activation of fibrinolysis with thrombolytics hastens resolution of perfusion defects right ventricle dysfunction, convincing benefi is lacking. As thrombolytics cause increased bleeding complications, including a 0,3–1,5 % risk of intracerebral haemorrhage, they are only recommended for life-threatening PE with compromised haemodynamics.

13. PLEURAL DISEASES

In clinical medicine, the pleura is important not only because diseases of the lung commonly cause secondary abnormalities in the pleura, but also because the pleura is a major site of disease in its own right. Not infrequently, pleural disease is a manifestation of a multisystem process that is inflammatory, immune, or malignant.

ANATOMY AND PHYSIOLOGY

The potential space between the parietal and visceral pleurae serves as a coupling system between the lung and chest wall, and normally contains a small amount of fluid. A negative pleural pressure is maintained by the dynamic tension between the chest wall and the lung. Both pleurae have a systemic blood supply and lymphatics, although lymphatic drainage of the pleural space is predominantly via the parietal pleura. Fluid flow through the pleural space is determined by Starling's relationship between microvascular pressures, oncotic pressures, permeability and surface area. Normally, there is net filtration of transudative (protein-poor) fluid into the pleural space that is balanced by resorption via the parietal lymphatics.
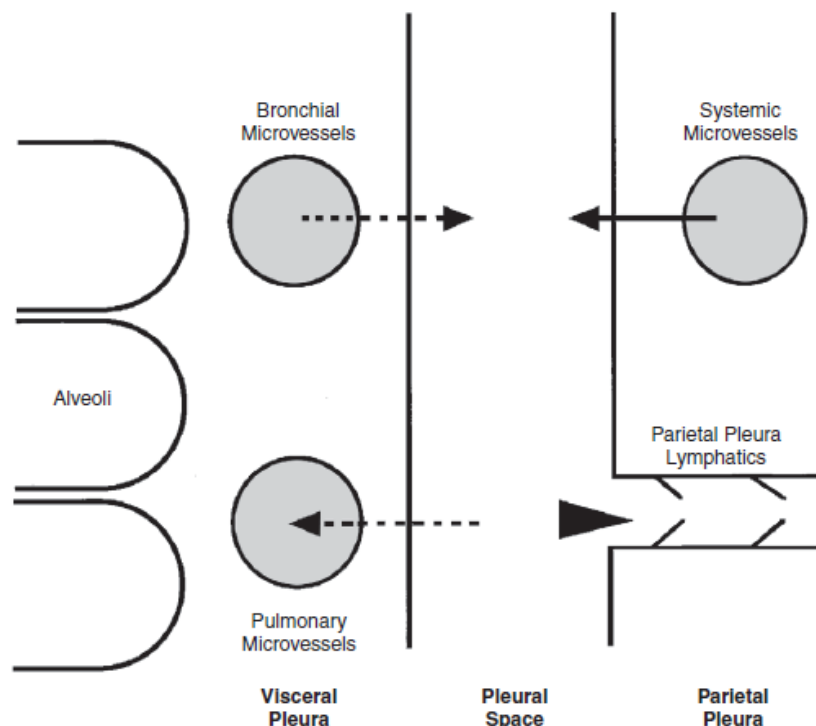

Figure 13.1 — Schematic diagram of normal filtration and resorption of fluid in pleural space. Solid arrow shows filtration of fluid from parietal pleural microvessels into pleural space. Arrowhead indicates removal of fluid through stomas and into parietal pleural lymphatics. Dashed arrows indicate a minor role for fitration and resorption of fluid by visceral pleural microvessels. (Adapted from Pistolesi M, Miniati M, Giuntini C: Am Rev Respir Dis 140: 825–847, 1989.)

PATHOPHYSIOLOGY

Most diseases of the pleura present with pleural effusion, which can be detected on chest X-ray when more than 300 ml of fluid is present. Effusions are due to excessive fluid formation or inadequate fluid clearance.

Types of pleural effusion

Transudative effusions are usually due to an imbalance in Starling's forces across normal pleural membranes, have protein-poor fluid are often bilateral and are not associated with fever, pleuritic pain or tenderness to palpation. The most common causes of a transudative effusion is congestive heart failure (table 13-1).

Exudative effusions imply diseases of the pleura or the adjacent lung (table 13-1) and may manifest as *pleurisy or empyema. Pleurisy* is term commonly used to describe the sharp localized pain arising from any disease of the pleura. It is limited inflammation of the pleura. *Empyema* is accumulation of pus.

Chylothorax is due to accumulation of triglyceride-rich lymph in the pleural space, generally as the result of damage to the thoracic duct causing leakage into the pleural space, for example due to trauma or carcinoma.

Hemothorax — blood in the pleural space, often secondary to trauma.

Table 13.1 — Causes of pleural effusions

Exudative (protein ratio pleural/serum >0.5 or LDH ratio pleural/serum >0.6 or pleural LDH >0.66 of top normal serum value)		Transudative (meets none of the criteria for exudative)
Infectious Para-pneumonic (bacterial pneumonia) Empyema Tuberculosis Parasitic • amoeba • echinococcus • paragonimus Viral **Autoimmune/collagen vascular** Systemic lupus erythematosus Rheumatoid arthritis **Neoplastic** Lung cancer Metastatic disease Mesothelioma	**Abdominal** Pancreatitis/pseudocyst Oesophageal rupture Liver abscess Splenic abscess **Miscellaneous** Pulmonary embolism Drug reactions Asbestos exposure Haemothorax Chylothorax Post-cardiac surgery Post-myocardial infarction Meig's syndrome	Congestive heart failure Cirrhosis Hepatic hydrothorax Myxoedema Nephrotic disease Peritoneal dialysis

CLINICAL FEATURES

Symptoms develop if the fluid is inflammatory or if pulmonary mechanics are compromised. The most common symptoms of a pleural effusion are chest pain, dull aching pain, fullness of the chest and dyspnea. They are made worse by deep inspiration and coughing.

Physical examination reveals decreased breath sounds, dullness to percussion, decreased tactile or vocal fremitus. If there is inflammation there may be a friction rub. Compressive atelectasis (partial lung collapse) may cause bronchial breath sounds.

DIAGNOSTIC APPROACH

The posteroanterior and lateral chest radiographs are clearly most important in the initial evaluation of the patient with suspected pleural effusion.

With a small effusion, blunting of the normally sharp angle between the diaphragm and the chest wall (costophrenic angle) is seen. With a larger effusion, a homogeneous opacity of liquid density appears and is most obvious at the lung base(s) when the patient is upright.

Ultrasonography is another technique frequently used to evaluate the presence and location of pleural fluid. Ultrasonography is particularly useful in locating a small effusion not apparent on physical examination and in guiding the physician to a suitable site for thoracentesis.

When pleural fluid is present and the etiologic diagnosis is uncertain, sampling the fluid by thoracentesis (withdrawal of fluid through a needle or catheter) allows determination of the cellular and chemical characteristics of the fluid. These features define whether the fluid is transudative or exudative and frequently give other clues about the cause.

Although different criteria have been used, the most common criteria include the levels of protein and of the enzyme lactate dehydrogenase (LDH) within the fluid, both in absolute numbers and relative to the corresponding values in serum. Exudative fluid has high levels of protein, LDH, or both, whereas transudative fluid has low levels of protein and LDH.

Pleural fluid obtained by thoracentesis is routinely analyzed for absolute numbers and types of cellular constituents, for bacteria (by stains and cultures), and for glucose level. In many cases, amylase level and pH value of the pleural fluid are measured. Special slides are prepared for cytologic examination, and a search for malignant cells is made.

In some cases, pleural tissue is sampled by closed pleural biopsy, generally performed with a relatively large cutting needle inserted through the skin of the chest wall. Histologic examination of this tissue is most useful for demonstrating granulomas of tuberculosis but also can reveal implants of tumor cells from a malignant process in some cases. Pleural tissue also can be obtained under direct vision with the aid of a

thoracoscope passed through the chest wall and into the pleural space; this has become the most definitive method for evaluating the pleural space for malignant implants.

TREATMENT

Treatment of pleural effusion depends entirely on the nature of the underlying process and usually is directed at this process rather than the effusion itself. In cases with a high likelihood of the effusion eventuating in extensive fi brosis or loculation of the pleural space, e.g., with an empyema or a hemothorax, the fluid is drained with a catheter or a relatively largebore tube inserted into the pleural space. If loculation has already occurred, then thoracoscopy or an open surgical approach may be necessary to break up fibrous adhesions and allow effective drainage of the fluid and full reexpansion of the lung.

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