Chapter 126: Infections

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Respiratory infections are quite common. In a 1989 survey of the number of acute conditions per 100 persons per year, 95 persons reported having acute respiratory conditions during the course of the year. Because of this frequency of occurrence, the otolaryngologist-head and neck surgeon can expect to be involved often in the care and treatment of patients with infections of the tracheobronchial tree. The goal of this chapter is to provide and overview of the more common types of tracheobronchial infections and to assist the surgeon in the diagnosis and management of these patients. A good working relationship with a pulmonary specialist is a great asset in the management of difficult cases because there is significant overlap between these two fields; interspecialty cooperation can be a very valuable resource. Nonetheless, the otolaryngologist-head and neck surgeon must be familiar with these problems in order to diagnose and treat patients with tracheobronchial tree infections. This chapter will discuss laryngotracheal, tracheobronchial, and bronchopulmonary respiratory infections.

History

An accurate and detailed history of the patient is of paramount importance in the diagnosis of all infectious disorders; tracheobronchial respiratory disorders are no exception. Factors such as age, smoking history, exposure to noxious fumes or general anesthetic agents, aspiration, general physical health, systemic disorders, cardiac disease, renal disease, or malnutrition must all be considered in the evaluation of patients with infections of the tracheobronchial tree. Pulmonary anomalies of developmental origin must be considered when treating patients with respiratory disorders, especially those that are chronic. Anomalies of the pulmonary artery or pulmonary vein or other vascular anomalies may also contribute to chronic respiratory conditions.

Exposure to persons with symptoms of respiratory infections can cause infections. Because many tracheobronchial and pulmonary infections occur as a result of exposure to animals, documenting the extent of each exposure is important. Many diseases are uncommon in the USA but are prevalent in third-world countries. A history of travel abroad may help to determine the cause of a particular disease.

Although most infectious diseases have systemic effects such as fever, malaise, headaches, and myalgia, documentation of the fever curve is helpful. The presence of a productive cough, with description of the color and quantity, should be noted. A history of hemoptysis is significant. Other medical problems that the patient may have must be addressed because they often determine the treagtment and care that the patient receives.

Physical Examination

An infectious process that involves only the laryngotracheal area or the large bronchi will reveal the normal vesicular sounds associated with alveolar filling. Upper airway noises called *rhonchi* may be present; these will change when the patient coughs. With pneumonitis or pneumonia, normal vesicular sounds are absent. Rales indicate an alveolar process. The

absence of airway sounds, increased vocal fremitus, and egophony are indications of consolidation. Retractions may be evident if upper airway obstruction exists. Examination of the nail beds and perioral area may reveal cyanosis. Fingerclubbing, common in chronic diseases, is rare in acutely infectious processes.

Diagnostic Studies

Arterial blood gas determinations are necessary if the possibility of hypoxia or hypercarbia exists. Chronic carbon dioxide retention, often found in chronic obstructive pulmonary diseases, changes the respiratory drive from hypercarbic to hypoxic. If excessive concentrations of oxygen are then given, the respiratory drive fails. Low-flow oxygen may be given, but care must be taken to observe for apnea.

Management

In managing diseases involving the tracheobronchial tree, supportive care is of utmost importance. Bed rest is often required for patients with acute infections. The institution of high humidity and rehydration assists in loosening the thick mucus in the airway. Control of pain is important, especially in patients with pleuritic chest pain, because splinting decreases alveolar ventilation and reduces the effective cough. Narcotic analgesics suppress the respiratory drive and are best avoided. Postural drainage helps to clear very thick bronchial secretions, particularly in the aged or infirm who have difficulty coughing or who have a weak cough. Control of fever makes the patient feel better and prevents problems associated with hyperpyrexia.

General Considerations

Host defenses

The tracheobronchial and bronchopulmonary system, like the gastrointestinal system, is exposed routinely to multifarious microbes. Healthy individuals harbor a diverse colonization of potentially pathogenic bacteria. Nonetheless, these bacteria do not penetrate host defenses the majority of the time. A formidable barrier exists in the normal host starting with the epithelial lining of the airways and air spaces, which is a very tight junction epithelium preventing the entry of microbes. The next line of defense is the lamina propria and the interalveolar connective tissue, which contains IgA-secreting plasma cells and tissue macrophages that lyse, opsonize, neutralize, scavenge invading organisms. The lumen of the airways is bathed in a mucus blanket that also has antimicrobial properties. Tracheobronchial secretions contain lysozyme, lactoferrin, interferon, as well as surfactant, which act as antimicrobial agents. The mucus blanket is actively propelled by the ciliary action of the respiratory epithelium to the external environment. If local barriers fail and pathogenic microbes penetrate the tissues, a complex integrated series of events called *inflammatory response* serves as the next line of defense. Vasoconstriction is followed by vasodilatation and increased blood flow. The inflammatory response is characterized by slow flow in the capillaries and results in a local extravasation of fluid and adherence of phagocytes against the capillary endothelium. Various mediators serve as chemotactic factors to attract more phagocytes. Specific antibodies as well as complement further act to neutralize pathogenic microbes.

Infections of the Laryngotracheal Area

Diphtheria

Diphtheria is a disease that primarily affects the upper respiratory tract from the area of the pharynx to the lower trachea. Diphtheria has been seen in worldwide epidemics throughout the ages. During the nineteenth century nearly half the people who acquired the infection died. At that time diphtheria was a major cause of childhood fatality, with children between the ages of 2 and 5 being the most affected.

Corynebacterium diphtheriae, a gram-positive, club-shaped, non-acid-fast aerobic bacterium, is the casual agent. The bacterium does not form spores and is not motile or encapsulated. Although it usually appears club-shaped in a Gram's stain, it may be pleomorphic. A grey pseudomembrane develops on the pharyngeal mucosa, which is diagnostic of diphtheria. Bacilli are often found within this pseudomembrane. The bacilli are often found within the gray pseudomembrane, which is diagnostic of diphtheria.

The culprit is actually a specific phage that is housed by the *C. diphtheriae.* This phage produces the toxin that causes the disease. This toxin is a two-part protein: the first part binds the toxin to the human cell, and the second part attacks it enzymatically, causing cell death.

Natural history

An incubation period of 2 to 4 days follows exposure; a low-grade fever and lymphadenopathy then develop. Headache, vomiting, and nausea are often associated with the malaise. Symptoms relating to the areas of involvement of the upper respiratory tract then appear. A physical examination often reveals the gray pseudomembrane firmly affixed to the posterior pharyngeal wall. Removal of this pseudomembrane causes bleeding because the so-called membrane is actually the outer layer of the necrosis caused by the toxin. In the past, the patient usually died as a result of suffocation: laryngeal involvement with inflammation and edema caused progressive airway obstruction, leading to hypoxia, asphyxiation, and death. The tracheobronchial tree may be affected with pseudomembranes and edema, which also contribute to the hypoxia and asphyxia.

Diagnosis

The diagnosis may be based on the physical findings just mentioned. If so, both supportive and antimicrobial care should be instituted. The actual diagnosis, however, should be based on the culture of *C. diphtheriae* from the pseudomembrane. Loeffler's medium is the best culture medium; laboratory identification of the toxin is also helpful.

Treatment and immunization

Reduction of the mortality rate and the frequency of cases is attributed to two major factors. In 1890 the Behring-Kitasato antitoxin was developed and proved helpful in the treatment of acutely infected persons. It was, however, a horse-serum antitoxin to which nearly 10% of the population is allergic. Administering erythromycin at 30 to 40 mg/kg/day

in four divided doses over a 2-week period or procaine penicillin at 600,000 units intramuscularly every 12 hours for 2 weeks helps to eliminate the carrier state but is not effective against the toxin once it is in progress. However, an effective immunization was developed by 1924. Currently, children and adults are routinely immunized against diphtheria and the disease is rarely seen.

In fact, in the USA there are only about 200 cases per year; these usually are from the older, unimmunized population. Unfortunately, because of the dramatic drop in case numbers, society has developed a relaxed attitude toward routine immunization against diphtheria. If aggressive attempts at maintaining a high level of immunization fails, diphtheria may once again become epidemic.

If there is any question about the presence of immunity, a Schick test should be administered. Diphtherial toxin is introduced subcutaneously, and the resultant area of inflammation and necrosis is observed. If no immunity exists, necrosis and inflammation will result; little or no reaction indicates that an immunity exists. The presence of immunity is a negative result on the Schick test; the absence of immunity is a positive result.

Pertussis

Whooping cough was a very serious medical problem during the eighteenth and nineteenth ceturies, affecting mostly neonates and infants. The causal agent is *Bordetella pertussis,* a nonmotile and gram-negative coccobacillus. It is encapsulated but not spore forming. Clinical cases of whooping cough may also be caused by *B. parapertussis* and *B. bronchiseptica.* In the clinical setting no differentiation exists, but serologic analysis may reveal these three distinct entitites.

After an incubation period of 2 weeks, the patient goes through a catarrhal stage with low-grade fever and upper respiratory symptoms. This stage rapidly progresses to a paroxysmal stage, in which the characteristic cough is first noted. The whoop is actually the inspiratory sound following a rough barking cough. During this stage fever is absent. The tracheobronchial tree is at least partially obstructed by masses of bacteria growing in the thick, tenacious mucus. After the paroxysmal stage there is usually a prolonged convalescent stage, with occasional reexacerbations into the paroxysmal type of cough. Supportive care is urgent. It is important to note that the initial reduction in the number of deaths from whooping cough occurred as a result of improved supportive care; the development of the vaccine came later.

Neonates may present with only choking and apneic spells. The paroxysmal cough is not noted. Young infants may not have the typical leukocytosis seen in children over 6 months of age.

The culture of *B. pertussis* must be done on Bordet-Gengou potato-blood agar and may be positive only if taken early in the course of the disease. The institution of antibiotics such as erythromycin and tetracycline does not change the course of the disease but helps to decrease the risk of contagion. Immunization, which began in the 1940s, has nearly eliminated whooping cough in the USA. Because of the associated morbidity of the vaccine, questions have been raised about its risk-to-benefit ratio: should children be vaccinated despite the

attendant morbidity, or should vaccination be eliminated altogether?

Laryngotracheobronchitis

Upper airway obstruction in children can be a frightening and potentially devastating process. Although many causes may be responsible, the most common is laryngotracheobronchitis, commonly referred to as *croup.* This disease is most often caused by virus and is seen most frequently in October through December. For some unknown reason, males are more often affected than females.

Previously, croup was believed to be caused by a bacterial pathogen. Parainfluenza 1 seems to be the most common pathogen, followed closly by influenza virus type A, but many other types of parainfluenza and influenza viruses, respiratory syncytial virus, adenovirus, rhinovirus, enterovirus, coxsackievirus, ECHO virus, and rheoviruses are possible etiologic agents.

Natural history

Before 1940 the course of laryngotracheobronchitis was not the same as it is now. After a short incubation period, upper respiratory symptoms such as coryza, cough, and sore throat appear. As the disease progresses, the croupy cough that distinguishes this disease becomes evident. This cough is a barking, seal-like cough that can be quite frightening. A fever usually accompanies it. Upper respiratory tract obstruction may develop. The degree of obstruction is highly variable, from only a small amount of nasal flaring and tachypnea to severe suprasternal and substernal retractions, use of accessory respiratory muscles, stridor, air hunger, and cyanosis. The child is usually quite frightened. Fatigue develops from the increased respiratory effort and contributes to the hypoxia. Any crying also increases respiratory effort and may be deadly for the acutely ill patient. The disease follows a 3- to 7-day course, with a gradual rise to peak airway obstruction followed by a gradual reduction in the swelling and improvement of the respiratory distress.

Before the 1940s this acute process seemed more progressive. At that time it was believed that bacteria were the chief pathogens and that a number of bacteria, including *Staphylococcus aureus, Streptococcus pneumoniae,* and *Haemophilus influenzae,* were involved. A bronchiolar and pneumonic type of picture was usually seen, with high fevers and frequent mortality. The use of antibiotics seemed to decrease the mortality and bacteria were believed to be the causative agents. Croup today seems to be a different disease from that seen at the turn of the century.

Differential diagnosis

Evaluation of the child with an acute upper respiratory tract obstruction must center on the differential diagnosis. Laryngotracheobronchitis in most cases is of mild to moderate severity and resolves rapidly with minimal supportive care. However, other diagnoses, such as epiglottitis, diphtheria, ingestion of a foreign body, and angioneurotic edema, must also be considered.

Epiglottitis. Epiglottitis has a more rapid onset than croup and usually affects children who are somewhat older than those affected by acute laryngotracheobronchitis. Within 4 to 12 hours the child with acute epiglottitis may progress from normal respirations and apparent good health to complete obstruction. The child with acute epiglottitis appears septic and drools excessively because swallowing is painful. Blood cultures may confirm septicemia and when positive usually show *Hemophilus influenza* type B. The diagnosis is most readily differentiated by a lateral soft-tissue radiograph of the laryngeal airway revealing the "thumb print" sign of a swollen, cherry-red epiglottis. The steeple-shaped appearance of the subglottic airway is suggestive of acute laryngotracheobronchitis.

Diphtheria. Diphtheria has already been addressed in this chapter.

Foreign body. The possible existence of a foreign body must be considered in the differential diagnosis of any upper respiratory tract obstruction in children and adults. A small piece of eggshell, plasti, or bone is often lodged in the subglottic area, causing what radiographically and clinically appears to be croup.

Angioneurotic edema. Angioneurotic edema occasionally mimics epiglottitis in the soft-tissue radiographs of the neck; however, it progresses even more rapidly than acute epiglottitis and, occasionally, the skin of the face swells.

Management

The therapy for laryngotracheobronchitis is by and large supportive. Humidity is the mainstay of therapy. On arriving at the emergency room, the child must be kept calm (and with his parents), examined rapidly by only one physician, and placed in a mist tent. The temperature of the mist should not be too cold or more agitation may result. Because being inside the mist tent can be frightening, the parent may hold the child to encourage relaxation. Sedation may help, but care must be taken not to decrease the child's respiratory drive. If the child becomes hypoxic, an increase of inspired oxygen concentration in the mist tent is necessary. Although antibiotics are often given, the cause of the condition is viral, so there seems to be no rationale for their use.

Steroids have been touted as an important part of the management of croup. In a number of well-documented studies conducted between 1964 and 1967, the efficacy of steroid treatment was disputed. The double-blind study conducted by Leipzig et al (1979) supports the use of steroids in laryngotracheobronchitis.

Administering steroids for the treatment of croup continues to be a debatable practice. First introduced by Jordan in 1964, the other mainstay of the therapy for croup is nebulized racemic epinephrine. Response is often rapid: improved breathing and, occasionally, cessation of stridor and retractions. However, its effect may be short-lived, so this treatment may need to be repeated numerous times. Because of the rebound phenomenon, a child who receives racemic epinephrine for laryngotracheobronchitis in an emergency room setting should be admitted to the hospital for close observation.

Today significant controversy still exists over the comparative efficacy of endotracheal intubation versus tracheotomy in the care of the child with croup. Although many centers support the necessity for tracheotomy in any child with severe obstruction, endotracheal intubation is well proven to be at least as effective, and the incidence of complications (eg, subglottic stenosis following intubation for laryngotracheobronchitis) is dramatically low. Usually a small endotracheal tube may be gently slipped between the vocal cords through the edematous slitlike opening in the subglottic airway. As the swelling resolves, more air leaks around the endotracheal tube. A trial extubation with use of racemic epinephrine as needed is then in order. Constant supervision by well-trained personnel in an intensive care unit is of utmost importance.

Tracheobronchial Infections

Influenza

At the turn of the century a pandemic raged across the world, leaving some twenty million people dead in its wake. The disease process called influenza carried with it a very high mortality. In 1918 and again in 1957, pandemics occurred. The etiologic agent, *Myxovirus influenzae,* exists in three types. Antigenic variations exist in these three groups, making vaccination soemwhat difficult. Major shifts in the antigenic variations follow a 2- to 4-year cycle.

M. influenzae is an RNA nucleoprotein enveloped in a lipoprotein shell. The virus enters the cell nucleus to replicate. The RNA is then found at the periphery of the cell.

Influenza is most commonly seen in the colder months of the year. Although nearly half of any population is infected, those who are at the greater risk for significant morbidity or mortality are the very young and the very old. Pregnancy and cardiopulmonary or renal disease also increase the risk of morbidity.

After a 3-day incubation period the disease is heralded by high fever and headache. Commonly the patient becomes prostrate with severe myalgia, headache, and malaise. These is a nonproductive cough, and on auscultation of the lungs, no rales or rhonchi are heard. Chest radiographs are most commonly normal. Prostration usually lasts about 3 days, and recovery occurs within the week. If the fever should persist beyond that period or if pneumonia develops, a greater risk of morbidity exists.

Therapy is primarily supportive. Bed rest and control of body temperature and pain is helpful. Antibiotics should be used only in the face of suprainfection. Vaccination of high-risk groups has been only moderately successful in the past years.

Bronchiolitis

Bronchiolitis is a disease process most commonly seen in children. Mucus obstruction in the terminal branches of the bronchi is believed to cause this relatively benign disease. Seen most commonly in the cold months of the year, bronchiolitis begins with a slow onset of upper respiratory tract symptoms, such as cough, fever, and irritability. As the process progresses, tachypnea, retraction, and dyspnea may develop, although chest radiographs and

white blood count are normal. Rales and wheezes may be heard. Pathologically there is a thickening of the wall of the bronchi, with plugging of the lumen by the thick secretions, which if allowed to progress may lead to pneumonia. The most common cause is the respiratory syncytial virus, followed by adenovirus. Treatment is supportive, unless suprainfection requires antibiotics.

Bronchitis

Acute tracheobronchitis is not an uncommon occurrence in the winter. Like most upper respiratory infections, its onset is marked with malaise, coryza, sore throat, and cough, but as the fever rises, there is an increase in secretions from the tracheobronchial tree and the cough becomes productive. As the inflammation of the tracheobronchial tree becomes more intense, the mucosa increases its secretory function; at the same time the infection reduces the ciliary action. The amount of desquamation is increased, and the thick mucus blanket is further intensified by the slow dehydration that accompanies the fever and the anorexia.

Upon culture, this mucus usually reveals *Streptococcus pneumoniae* or *Staphylococcus* species. *Mycoplasma pneumoniae* is another common pathogen. If the process is severe, chest radiographs may be necessary to distinguish it from pneumonia. Pertussis, scarlet fever, typhoid, the viral pneumonitis of measles, and influenza must be included in the differential diagnosis.

Exposure to noxious gases and pollution have been touted as risk factors in the general population, but others are perhaps more important. Smoking increases the mucus blanket and decreases the action of the cilia. Persons having chronic obstructive pulmonary disease or those in a protein-wasting state are also at risk.

Therapy is both supportive and antimicrobial. Warm mist, bed rest, and control of both cough and fever are very helpful. Mucolytic drops help to thin the secretions and clear the airway. Antitussives may allow for improved sleep. Penicillin and ampicillin are the drugs of choice until culture results are obtained.

The use of bronchodilators seems to thin the mucus blanket and improve ciliary transport. Postural drainage is of great assistance for the elderly and weak. Sedatives should be avoided because they may decrease the respiratory drive. If supportive oxygen therapy is used, frequent monitoring of blood gases is needed. Endotracheal intubation may occasionally be necessary for control of tracheal and bronchial secretions.

If mucus production becomes chronic, malignancy, bronchiectasis, and cystic fibrosis must be ruled out. Tuberculosis must be considered in the person with chronic productive sputum.

Bronchopulmonary Infections

The next section reviews a number of disease processes that affect the lungs themselves. In general, the same diagnostic hallmarks exist. Decreased vesicular breath sounds, with either fine rales early in the course of the disease or absent breath sounds as consolidation develops, accompany increased vocal fremitus and egophony. Consolidation,

segmental collapse, and coin or cavity lesions may be seen on chest radiographs.

A culture is vital in accurately determining the etiology of any pulmonary process. The lower tracheobronchial or pulmonary area contains no normal flora. A sputum sample is the classic way of obtaining a culture. The patient with a productive cough should expectorate the coughed-up bolus of mucus. The speciment must then be immediately delivered for plating. Because the specimen has traversed the mouth, which is normally laden with bacteria and whose indigenous biota includes aerobes, anaerobes, and yeasts, careful investigation is necessary before a diagnosis is made.

Transtracheal aspiration is a safe, effective means of obtaining an unmasked culture. The patient is placed in the supine position with the head extended. The anterior neck near the larynx and upper tracheal rings is prepared with an antiseptic. Local anesthetic is then used to anesthetize the neck and trachea. Palpation of the prominent thyroid cartilage is a guide for determination of the proper position. A large-bore needle is inserted through the cricothyroid membrane and down toward the carina and the thick mucus is aspirated. Occasionally, saline lavage is required to obtain the thick mucus.

The sterile technique used in the introduction of the needle and the use of saline that does not have a bacteriostatic agent are crucial. A Luki tube is occasionally needed to collect the aspirated material without contamination. A bronchoscopic examination with lavage for culture and cytology is indicated if there is a question of carcinoma or if mucus plugging requires it. A brush biopsy may also be performed.

Pneumonia; general considerations

Pneumonia is considered the most common life-threatening infectious disease. The elderly ambulatory patient who presents to the emergency room with a fever is particularly likely to have a serious pneumonia and, in most instances, to require hospitalization. A study of young healthy navy personnel revealed that pneumonia had been found to be the major medical cause of lost work days. Pneumonia continues to be associated with high morbidity and prolonged costly hospitalization, particularly when it is nosocomial in origin. Pleural pulmonary infection remains the fifth most common cause of death in the USA accounting for an estimated 55.000 deaths annually.

Organisms can enter the lung and produce infections via various routes: the tracheobronchial tree, the pulmonary vasculature, and through the direct spread of infection from the mediastinum across the diaphragm and chest wall. Despite the fact that there is overlap between these situations, each one possesses morphologic findings that are sufficiently characteristic to be recognized roentgenographically and pathologically; this can be helpful in determining the specific causes of a given case of pneumonia. A review of these three routes of infection will be useful in the study of any patients suffering from these conditions.

The tracheobronchial tree route

Aspiration or inhalation of microorganisms often produces infection by way of the tracheobronchial tree. In rare cases, direct implantation of an organism by the use of a contaminated bronchoscope may result in direct infection of the airway. It is important to

emphasize that deposition of contaminated particulate matter is one of the main causes of infection of the respiratory tree. Coughing or sneezing by an individual who is either colonized or infected with microorganisms releases millions of water and mucus droplets that contain the infectious organism, be it bacteria or virus. When these droplets hit the air they rapidly lose water and become "droplet nuclei", which, due to their small size, can remain suspended in the air for long periods of time. Usually, inhaled droplet nuclei larger than 5 microm are deposited on the upper airways and those smaller than 0.5 microm are exhaled. Those in the intermediate range of between 1 to 2 microm are likely to become deposited on the bronchial or alveolar epithelium where they provide a focus for infection. There exists wide variation in the number of organisms needed to produce infection.

Even very small numbers of *Mycobacterium tuberculosis,* for example, can produce disease, whereas other organisms require a higher inoculum. Person-to-person contact may not be necessary for transmission of these pathogenic organisms because the small droplets can remain suspended for long periods of time; studies have shown that exposure to contaminated air for long periods of time can result in infection. Some organisms, such as the *Histoplasma capsulatum* or *Coccidioides immitis,* can be inhaled as air-borne particles that originate from contaminated soil.

Aspiration pneumonia occurs often from contaminated oropharyngeal secretions or gastrointestinal contents rather than from the aspiration of exogenous liquids. The normal adult oropharyngeal flora contains a variety of microorganisms; there are estimated to be 107 aerobic and 108 anaerobic species. Two of these are commensals with low virulence but some such as *Actinomyces israelii* and other anaerobes can cause pulmonary infection. In hospitalized patients a further threat is presented by gram-negative bacteria that may inhabit the airways of chronically ill hospitalized patients.

Change in bacterial flora towards more virulent forms occurs to a significant extent in patients receiving antibiotics in intensive care units. In such situations, aspiration of even small quantities of contaminated saliva or nasal secretions can result in a sufficiently high bacterial inoculum to result in infection.

Pneumonia acquired via the tracheobronchial tree can be subdivided into three main pathogenic types: Air space or alveolar pneumonia is characteristic of pneumococcal *(S. pneumoniae)* infection but it can also be seen with other organisms such as *Klebsiella pneumoniae.* The most important pathogenic feature of this form of pneumonia appears to be the rapid production of edema with relatively minimal cellula reaction. The edema tends to localize initially in the periphery of the lung beneath the visceral pleura. The fluid flows directly from alveolus to alveolus as the amount increases. The radiologic appearance of this type of infection is a homogenous consolidation that is relatively sharply demarcated from the juxtaposed uninvolved parenchyma. The larger airways remain patent and this creates the appearance of an air bronchogram. The second type of pneumonia pattern is bronchopneumoniae or lobular pneumonia. This infection if typified by *Staphylococcus aureus* and it differs pathogenically from air space pneumonia in that a relatively small amount of fluid is produced by the rapid exudation of polymorphonuclear leukocytes in the terminal airways. These leukocytes prevent the spread of organisms at least initially and give the disease a distinctly patchy appearance. The third type, interstitial pneumonia, is caused

typically by viruses or *Mycoplasma pneumoniae* and is characterized by inflammatory cellular infiltrate and edema that is located predominantly within interstitial tissue. The underlying pathogenesis is related to the alveolar capillary membrane and in particular to the alveolar epithelium. Consolidation of full lobules can result if the disease is extensive, effectively obliterating the interstitial pattern at the gross level and simulating air space pneumonia.

Pulmonary vasculature route

Infection via the pulmonary vasculature is usually a result of an extra pulmonary focus of infection with a resultant septicemia. Because of gravity, infections occurs primarily in the dependent portions of the lung, particularly in the basal aspects. Roentgenographically, infection via the pulmonary vasculature is often characterized by a nodular appearance of the individual foci of infection. Rarely, there can be seeding, which results directly from an intrapulmonary focus of infection into a pulmonary artery; this may occur, for example, in tuberculosis. The disease resulting from an intrapulmonary focus of infection shows a specific distribution in the lung parenchyma supplied by that vessel. It is most likely that organisms exit the circulation from pulmonary arterioles, venules, or capillaries so that the pattern of parenchymal involvement tends to be patchy and shows a random distribution in the early stages of disease.

Infection by direct spread

Penetrating thoracic trauma or wounds can result in direct spread of infection across the chest wall or diaphragm or from the mediastinum. Extension of infection from an extrapulmonary source, such as a diaphragmatic abscess or mediastinitis (such as may result from esophageal rupture), may also result in infection by direct spread. In these cases, the infection in the lungs usually will take the form of an abscess adjacent to the source of infection.

Bacterial pneumonias

The most common cause of death secondary to an infectious process is by bacterial pneumonia. It also ranks in the top ten most common causes of death in this country. In spite or all of the advances of modern medicine, nearly one of every ten admissions to hospitals in the USA is for a bacterial pneumonia. The most common causal agent is *Streptococcus pneumoniae*, which far outranks all the other causes of bacterial pneumonia. Other causal agents include *Klebsiella sp, Staphylococcus aureus,* and *Haemophilus influenzae.* Although there are many others, they comprise much less than 1%. Respiratory inhalation and hematogenous spread are the two most likely routes of entry.

Etiology

Many factors contributing to the development of a bacterial pneumonia. Viral upper respiratory tract infections decrease the activity of the cilia, decreasing the normal flow of the mucus blanket. This increases mucus production and decreases alveolar macrophage activity. Those with chronic obstructive pulmonary disease already have most of the microscopic risk factors and therefore are at constant risk for the development of a bacterial pneumonia. With uremia or metabolic acidosis, immunologic defenses decrease. The aspiration of gastric

contents changes the pH, causing a chemical injury. Food particles may also obstruct the bronchi. General anesthesia contributes to the risks. The noxious gases seem to affect the immune defenses adversely, and the drying effect on the respiratory epithelium is also deleterious. The placement of an endotracheal or tracheotomy tube increases mucus production.

Natural history

Pneumococcal pneumonia. Pneumococcal pneumonia is heralded by the sudden onset of shaking, chills, and high fever. Often a patient is able to document the onset to the hour and minute. In spite of the fact that fever and chills predominate, rigors are rarely seen. Because of the pleuritic chest pain associated with pneumococcal pneumonia, splinting and alveolar hypoventilation occur. Chest radiographs are diagnostic of a pneumonia usually affecting a lobe or segment. Type 3S *S. pneumoniae* is associated with an extremely poor prognosis. If leukopenia is also noted, aggressive therapy must be instituted rapidly.

Staphylococcal pneumonia. If the etiologic agent is *S. aureus*, the disease usually progresses usually much more rapidly. Significantly necrosis of lung parenchyma often accompanies respiratory compromise, leading to death in 8 to 12 hours. Abscess formation is common. In spite of aggressive medical care, both supportive and antimicrobial, the fatality rare is extremely high.

Klebsiella pneumonia. Klebsiella pneumonia is also an extremely devastating disease. The rapidity of the progression from a relatively normal state of health to death may be prompt. This pneumonia is usually seen only in those with significant underlying diseases.

Management

The management of bacterial pneumonias relies on both vigorous supportive care and the use of antimicrobial agents. Hydration to improve the flow of the mucociliary blanket is often best accomplished with intravenous fluids. With the accompanying malaise, myalgia, and fever, bed rest is appropriate. It is important to control the patient's temperature with antipyretics. If the patient becomes hypoxic, oxygen may be used as needed. Occasionally the patient experiences a pleuritic type of chest pain. Control of pain is important for the maintenance of the inspiratory effect needed to ventilate the lungs adequately and to assist in clearing secretions. Narcotic analgesics should be avoided because of their respiratory depression. Nonnarcotic analgesics and nerve blocks may be helpful. The maintenance of an adequate caloric load is important, especially in the debilitated patient who has muscle wasting. Bronchodilator therapy improves mucociliary transport, has mucolytic properties, and corrects reversible airway disease. If the disease process continues and the thick bacteria-laden secretions cannot be mobilized, endotracheal tube placement should be considered.

Antibiotic therapy must be based on culture and sensitivity results. Gram's stain and fungal and acid-fast stains may allow for early direction in therapy. Intravenous penicillin G should certainly be administered in most cases of pneumonia. If gram-negative organisms or anaerobes may be the causative agents, additional drugs can be added. The severely toxic patient is best treated by multiple antibiotics, pending the results of transtracheal aspiration.

Nocardiosis

Although for years *Nocardia* was considered to be fungus, the existence of a bacterial form has been established. Three major species of *Nocardia* are found in human pneumonic processes: *Nocardia caviae, N. brasiliensis,* and *N. asteroides.* These acid-fast bacilli are aerobic and gram positive. They have no capsule and are nonmotile. They occasionally but not always form filaments as they grow. As regard classification, they are similar to *Actinomyces* and *Mycobacterium.*

The pneumonitis from the nocardiae progresses over time to necrosis and abscess formation. Although the nocardiae may then embolize to all organs, the most noteworthy is the brain. Microemboli may develop even if only a small pulmonary lesion exists. Nocardiae often have very little inflammatory response in the lung, and the course of the disease may be indolent.

Nocardiae are saprophytes, and it is thought that they become pathogens as they are inhaled through the respiratory tract, although nocardiosis is not a disease of the healthy. If the patient is unresponsive to normal therapeutic agents, nocardiosis should be suspected. The only true way to diagnose a *Nocardia* pulmonary infection is to isolate the organism.

Sulfonamides are occasionally administered, combined with trimethoprim. Gentamicin, although effective for pulmonary lesions, is not as effective for central nervous system microemboli. Measuring the blood concentrations of the sulfonamide is very important to ensure a therapeutic range of 12 to 15 mg/100 mL.

Actinomycosis

The hallmark of an actinomycosis infection is a chronic granuloma with sulfur granules. *Actinomyces israelli* has been considered a fungus for many years but is actually a bacterium. The rods often branch, giving it a fungal appearance, but it is a gram-positive bacillus. Actinomycosis is often in normal residence in the tonsillar crypts and gingivodental sulci; the diagnosis by culture should therefore be from a transtracheal aspirate. *Actinomyces* causes a low-grade pneumonitis with a nonproductive cough. As the disease progresses, however, the cough becomes more productive, and often hemoptysis is seen. Necrosis, empyemas, and sinus tracts soon develop. The sinus tracts often break through to the skin, pleaura, heart, and thoracic vertebrae, or go through the diaphragm to crease suprahepatic or perinephric absesses. The sulfur granule is often but not always present.

The most important factor in establishing this diagnosis is to consider it in the differential diagnosis. The culture must be taken under anaerobic conditions. The treatment may require 2 to 3 months of constant antimicrobials. Penicillin is the drug of choice and should be administered intravenously until the lesion disappears. Thereafter it may be continued in an oral form. Tetracycline is an acceptable drug as well.

Mycoplasma pneumoniae

Primary atypical pneumonia is caused by an agent at first felt to be a virus but later determined to be a bacterium. It had been called the pleuropneumonia-like organism (PPLO). In 1942 Eden first isolated *M. pneumoniae.* The bacteria were found to have no rigid cell wall. This microaerophilic organism ferments glucose, has very stringent requirements for culturing and requires an artificial medium. If the organism is cultured, it may take as long as 2 to 3 weeks to obtain results. Because it has no cell wall, it is resistant to any penicillin but may be sensitive to tetracyclines.

The typical pneumonia seems to be more prevalent in winter and is seen mostly in youth. The incubation period may be as long as 2 weeks. An upper respiratory syndrome then appears with chills, fever, and cough. The white blood count is normal. Chest radiographs often reveal a pneumonia.

Diagnosis may be indicated by a positive cold agglutinin test at a factor of 1 to 32. Most often by the time the organism is grown in culture, the patient is better. It is rarely fatal, but the patient may develop additional side effects. Almost one in five develops a pleural effusion, and some develop an autoimmune hemolytic anemia. A well-documented hemolytic crisis seems related to the rapid diminution of skin temperature when the patient receives a sponge bath to treat temperature elevation.

The use of antimicrobials seems to decrease the duration of symptomatology. Tetracycline is the drug of choice, followed by erythromycin.

Pulmonary Mycobacterial Infections

Tuberculosis

In the seventeenth and eighteenth centuries tuberculosis devastated Europe. It is estimated that this disease accounted for nearly one third of all the deaths at that time. Although it has certainly declined over the past centuries, tuberculosis remains an important pathogen in our society.

Natural history

Mycobacterium tuberculosis, an obligate aerobe, is an acid-fast bacterium that is noncapsulated and nonmotile. The dividing time of the mycobacterium is so slow that often 1 month is required before a culture shows the organism. It is transmitted by particle droplets through the respiratory tract. The disease is then usually indolent for years but may show up as a cavitary lesion, most commonly in the apical lobes of either lung.

As the mycobacterium is implanted into the alveolar area, an inflammatory reaction is first established, followed by a surrounding tubercle. Caseation then takes place. Often this localized disease spreads by contiguity to the pleura, adjacent lung, or pericardium. Occasionally the spread may be revealed by spillage of material from the tuberculoma through the bronchi. Lymphatic and hematogenous spread is also common. Miliary tuberculosis is a defined process in which the metastatic foci are scattered in small tuberculomas throughout

the entire body. The liver may be riddled with small tubercles the size of millet seed. The chest radiograph may be dotted in a similar fashion.

Diagnosis

Although the typical chest radiographic appearance has a cavitary nodule, coin lesions, or multiple soft fluffy nodules, diagnosis requires isolation of the mycobacterium. If acid-fast bacteria are seen in the smear, treatment should usually be instituted as one awaits the culture. The presence of a recently converted tuberculosis skin test - purified protein derivative (PPD) - may also be helpful but again is not diagnostic.

Management

In the past, therapy was restricted to bed rest or placing the patient in a sanatorium. This of course was not particularly successful, although in the natural course of the disease the tuberculoma was often walled off, and the patient survived. Today many drugs are available that have proven efficacious in the treatment of tuberculosis; ethambutol, rifampin, isoniazid (INH), and streptomycin are the most common ones used. Because of the extremely slow rate of mycobacterium division, treatment over a long duration is necessary to eradicate the disease. Although INH may be taken orally, ethambutol and streptomycin are usually given in an intramuscular injection. The addition of rifampin for the patient with active tuberculosis has improved patient cooperation because rifampin may be taken orally as well. Rifampin is associated, however, with hepatic toxicity, so one must be careful to observe liver function while the patient is taking this drug.

Serial sputum specimens establish a duration for initial treatment when no further acid-fast organisms are seen. Serial radiographs may document the resolution of tuberculosis. Most therapy courses last up to 2 years if an oral regimen is preferred. INH is given at 5 to 10 mg/kg/day and rifampin at 10 mg/kg/day in one oral daily dose. This may be given for the entire 24-month period. If hepatic toxicity appears, one must change to ethambutol in a twice-weekly intramuscular injection. If streptomycin is used, care must be taken to document the auditory and vestibular function. Chemoprophylaxis is recommended for family members. INH taken at 300 mg/day is given to each adult, and children should take 10 mg/kg/day in a single daily oral dose.

Other mycobacterial diseases

Pulmonary diseases identical to tuberculosis may arise that are not caused by *Mycobacterium tuberculosis.* Some 14 additional species of *Mycobacterium* exist, each of which may cause a similar pulmonary disease and in addition may be seen to affect the skin or cause cervical adenitis. Occasionally the PPD is positive, but only a culture can definitively establish the diagnosis. Included are *M. avis, M. kansasii, M. intracellulare* (the Battey bacillus), and *M. scrofulaceum.*

Lung Abscesses

Anaerobes most commonly cause lung abscesses. Although anaerobes are normal oral cavity flora, because of the usual position of a lung abscess (the posterior segment of the right upper lung, the posterior segment of left upper lung, or the apical segments of the right or left lower lungs), aspiration is thought to be a major cause. Other possible causes include chest trauma, pulmonary emboli, and bacteremia. If a foreign body or cancer obstructs a bronchus, an anaerobic lung abscess may form distal to that obstruction and therefore may occur in any lung segment.

Apart from the normal manifestations of a pneumonia, the cough brings forth copious amounts of foul-smelling sputum. A sputum culture alone usually does not allow accurate assessment because anaerobes are common oral cavity flora. A transtracheal or bronchoscopic aspiration is required. If bronchoscopy is performed, a brush biopsy and specimen for cytology must be obtained to rule out carcinoma. The differential diagnosis includes gram-negative pneumonias, tuberculosis, and bronchiectasis. Often the anaerobic abscess may form an empyema or a bronchopleural fistula. Mortality is high.

Penicillin G is usually very effective in the treatment of most anaerobes of the oral cavity, but other types of penicillin and cephalosporins are much less active. Treatment regimens should initially include chloramphenicol because of the possible presence of *Bacteroides fragilis,* which is resistant to penicillin; carbenicillin is also effective against *Bacteroides fragilis.* Antibiotics may be altered after a specific culture has been obtained. Bronchoscopy is useful in draining pulmonary abscesses. The bronchoscope is pushed through the cavity wall, and the debris and pus are aspirated from the cavity. Repeated endoscopy may be necessary before resolution occurs.

Psittacosis

Parrots, parakeets, cockatoos, turkeys, and pigeons all are carriers of *Chlamydia* species. These organisms are intracellular parasites. In humans the organisms may cause cell lysis. A 2-week incubation period is followed by sudden onset of high fever and headache. Pneumonitis causes a productive cough and often hemoptysis. One in twenty people with this disease dies. Antibiotic treatment with tetracycline or chloramphenicol must be accompanied by extensive supportive care. One can isolate the organisms by injection into hen's eggs, but the diagnosis is usually made by antibody testing. To curb the incidence of psittacosis, commercial birds, such as turkeys, are fed tetracycline to reduce the prevalence of chlamydial contamination. Restriction of the import of certain foreign avian species is also helpful.

Q Fever

Q fever is a rickettsial disease caused by the very hardy *Coxiella burnetii.* Rickettsiae are maintained in a tick vector harbored by both cattle and sheep. *Coxiella* resists desiccation and high temperatures as well as formaldehyde and phenol. It is thought that the disease is transmitted by inhaling particles containing the rickettsiae. The incubation period may be as long as 3 weeks; fever, chills, malaise, and headache then appear. Most people experiencing Q fever have pneumonitis. Rarely do people die of this self-limiting disease, but treatment with tetracycline and/or chloramphenicol reduces the symptomatology and the carrier state.

A diagnosis may be made by the growth of the rickettsia in the guinea pig, but a serologic test is usually diagnostic.

Histoplasmosis

Disseminated histoplasmosis is a devastating disease. *Histoplasma capsulatum* is a fungus that has both yeast and hypha forms. Spores exist in the later form. Although the respiratory illness caused by the inhalation of histoplasmosis may be mild, in infants and the aged it may progress to a very severe multiorgan disease with an extremely high fatality rate. If the disease is limited to the lungs, a chronic cavitary disease is present. Fatality with pulmonary disease approaches 20%.

The diagnosis must be entertained because isolation of the fungus is required for diagnosis. Skin testing, although available, is not helpful in the diagnosis of the acute histoplasmosis. A definite rise in histoplasmosis titers is suggestive but not diagnostic. Therapy requires intense supportive care and occasionally surgical excision of the lung mass. Pericadial involvement with cardiac constriction is not infrequent. Treatment with amphotericin B for 10 weeks is required.

Coxiella Mycosis

Coxiella mycosis has also been called valley fever, San Joaquin fever, and coccidioidomycosis. Its cause is *Coccidioides immitis,* a fungus usually found in the spherule form in its host. As it is grown in a medium, it becomes mycelial with septated hyphae. The fungus is contagious, especially to those trying to culture it in the laboratory. *Coccidioides* is found in many semiarid areas across the world. Usually the summer is hot and the winter is moderately wet with infrequent freezing. *Coccidioides* is endemic to areas of California (most notably San Joaquin valley), Arizona, Texas, and New Mexico. It is also noted in Mexico, Honduras, Venezuela, Colombia, and Argentina.

Although most of the people in these areas have been infected, only about one in a hundred is symptomatic. Dissemination is rarely seen in whites but is more commonly seen in blacks and Filipinos. Pregnant women are at great risk for dissemination of this disease. After a 1-month incubation period, night sweats, chest pain, headaches, cough, and fever develop. With the pneumonitis, hemoptysis usually exists. Erythema nodosum or erythema multiforme is occasionally found.

One must consider the diagnosis. Microscopic evaluation of the pus may reveal the spherules, but cultures could take weeks. Serial serology helps to monitor the course of the disease and assist in establishing a diagnosis. Extrapulmonary dissemination, as well as the severe primary pulmonary disease, must be treated with amphotericin B. If the diagnosis is established for a pregnant woman in her third trimester, amphotericin B is suggested because of the high risk of disseminated disease. If the disease is less severe, conservative treatment with bed rest and supportive care is usually all that is necessary.

Aspergillosis

The *Aspergillus* species may create an invasive pulmonary infection. These hyphae lodge in the bronchiolar area and invade through the bronchiolar walls. Because of the aggressive invasion, they rapidly disseminate hematogenously. This invasive pulmonary process is different from a fungus ball. The fungus ball in a bronchus or paranasal sinus may be easily treated by excision alone. Diagnosis is extremely difficult because of the ubiquitous nature of the branching hyphae. In disseminated aspergillosis, amphotericin B may not be effective except in an extremely high dosage. Usually the disease is fulminant and fatal.

Blastomycosis

Blastomycosis is a slowly progressive pulmonary disease with an occasional spontaneous remission. The yeast form, *Blastomyces dermatitidis,* may also be found in a hyphae spore-forming state. It is a disease of middle-aged men. It is usually insidious in onset but eventually presents with hemoptysis, chest pain, fever, and night sweats. The chest radiograph may show anything from a small pulmonary infiltrate to cavitary disease. Diagnosis must be made by culture. Therapy is the same as in other fungal diseases: supportive care and administration of amphotericin B.

Candidiasis

The *Candida* species are nearly ubiquitous in the human. Almost half of all people have *Candida* organisms as normal oral or gastrointestinal microflora. These dimorphic fungi have both a yeast and a hyphal form. They can be cultured on blood agar. Usually they do not contribute to a disease process unless some breakdown occurs in the normal barrier of spread of infection. A person in an immunodeficiency state is especially at risk. Patients with central venous lines for total parenteral nutrition or antibiotics may develop candidiasis secondary to a contaminant in the intravenous solution. A protein-wasting or severe surgical or medical disease increases the risk. Typically the outcome of the *Candida* infection is related to the underlying disease process. Diagnosis is made by culture of these organisms.

Therapy must initially be addressed toward correcting the underlying disease process. Systemic therapy, as for all fungal infections, is amphotericin B. One must continually monitor the plasma levels of amphotericin B to ensure a proper therapeutic range.

Viral Pneumonias

Viral pneumonias are not uncommon in the pediatric and adult age groups. Children usually have a respiratory syncytial virus or a parainfluenza virus as the cause. In the adult population influenza and adenoviruses are most common. In addition, varicella, measles, and variola may cause pneumonitis and may progress to primary bronchopneumonia. Cytomegalic inclusion virus is a common cause of pneumonitis in the immunodeficient patient. No specific therapy apart from supportive therapy exists for this condition.