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Pulmonary Infections

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Usual Pneumonias Caused by Gram-Positive and Gram-Negative Bacteria

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Practically any microorganism can cause pneumonia, particularly among the immunocompromised. This chapter focuses on a select group of gram-positive and gram-negative bacterial pneumonias that, because of their frequency, are highly relevant to general clinical practice and pathology. They are presented in Display 38-1.

A well-performed and properly interpreted Gram stain of a smear of deep sputum from a patient with clinical and radiographic features of acute respiratory infection frequently provides a rational approach to antibiotic therapy.[1,2] The same applies to tissue sections of lung exhibiting inflammatory changes suggestive of bacterial infection; this is particularly important in immunocompromised patients who frequently present with mixed infections or with atypical or missing inflammatory responses to tissue invaders.

Yet it should be clearly stated that the task of establishing the etiology of an infectious pneumonia rests, frequently and ultimately, on appropriate cultures of the organism or organisms; thus, the importance of a close communication between pathologist and microbiologist cannot be overemphasized. It is also clear that an ever-increasing number of clinical laboratory tests, including the application of modern tools of molecular biology, have brought enormous benefits to patients because of a timely, reliable diagnosis that frequently obviates biopsy. The potential diagnostic value of such an approach can only be guessed at the present time. Nevertheless, for those involved in the pathologic diagnosis of pneumonia, clinical tests, whenever available, should provide a gold standard to check the validity of the histologic findings.

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GRAM-POSITIVE PNEUMONIAS

Pneumococcal Pneumonia

The advent of antibiotics brought a marked decrease in mortality and complications as a result of pneumococcal pneumonia. However, *Streptococcus pneumoniae*—the etiologic agent of this infection—still accounts for as much as 60% of all cases of culture-proven acute pneumonias and for as many as 500,000 annual cases in the United States.[3] The most frequent extrathoracic complication of pneumococcal pneumonia today is bacteremia, present in 25% to 30% of the cases;[4] 89% of patients with pneumococcal bacteremia have demonstrable pneumonia.[5] The case fatality rate from pneumococcal pneumonia is 5% to 10%, but in the presence of bacteremia it can be as high as 30%.[4,5] In developing countries, pneumococcal pneumonia poses a major threat to children's survival.[6]

The clinical picture of pneumococcal pneumonia, first recorded by Osler,[7] is an illness of sudden onset with high fever, chills, dyspnea, chest pain on the affected side, and productive cough of abundant sputum that is readily expectorated. The sputum is thick, tenacious, green, and blood-tinged, and Gram-stained smears reveal abundant polymorphonuclear leukocytes, erythrocytes in various stages of degeneration, and numerous gram-

DISPLAY 38-1. COMMON BACTERIAL PNEUMONIAS

Gram-Positive

Pneumococcal pneumonia
Streptococcal pneumonia
Staphylococcal pneumonia
Diphtherial pneumonia

Gram-Negative

Haemophilus influenzae pneumonia
Serratia pneumonia
Pseudomonas aeruginosa pneumonia
Klebsiella pneumonia
Escherichia coli pneumonia
Bordetella pertussis pneumonia (whooping cough)

positive lancet-shaped diplococci with abutting flattened ends. The small cocci predominantly occur in pairs and short chains.

The microorganisms are fastidious, fragile, and rapidly killed by drying or extremes of temperature. Successful isolation from sputum samples requires prompt plating of the fresh sputum on blood agar plates, but even in samples optimally handled and containing numerous gram-positive diplococci in sputum, the cultures may be negative.[3]

Pathologically, pneumococcal pneumonia may be lobar or lobular in anatomic distribution.[8] The pathologic findings, in the absence of antibiotic therapy, were best described by MacCallum in autopsies of victims of the influenza epidemic of 1919.[9] He recognized and carefully described cases in which *S. pneumoniae* was isolated in pure culture as the only demonstrable pathogen.

The gross and microscopic pictures of pneumococcal pneumonia vary according to the clinical stage. In well-established cases, it is a typical acute lobar or lobular process progressing from red to gray hepatization, but it is indistinguishable from similar patterns in other bacterial pneumonias.

Death during the early acute phase usually reveals little fluid in the thoracic cavity and slight dulling of the parietal pleura with yellow flecks of fibrin. The visceral pleura is usually unremarkable. The consolidated lobules are sharply outlined on the pleural surface and alternate with air-containing and atelectatic lobules; they are less distinct when the process becomes confluent. Areas of consolidation are common on the posterior and lower parts of each pulmonary lobe, most frequently on the lower lobes.

Sections of the lungs reveal few abnormalities of the bronchi and unremarkable blood vessels. The bronchi are usually empty or partly filled with a thin, brownish or blood-tinged frothy fluid, and the mucosa is usually unremarkable. The cut surfaces of the lungs show a parenchyma that is firm and elastic, and on pressure it exudes abundant blood and edema fluid.

Microscopically, in areas of early consolidation, extraordinary dilatation of the septal capillaries can be seen, and the alveolar ducts contain clear fluid with few leukocytes and a delicate coagulum. The alveolar ducts are also lined by hyaline membranes that often run into neighboring alveoli. The alveolar walls are well preserved, and the air spaces contain fluid with leukocytes, mononuclear cells, and numerous erythrocytes held together by a delicate meshwork of fibrin. During the early stage, pneumococci are numerous throughout and easily found on Gram-stained sections.

In later stages of pneumococcal pneumonia, the picture is one of extensive consolidation. Every stage of consolidation can be observed, but most characteristic is the classical lobar pattern of firm red or gray hepatization (Color Fig. 38-1). The latter patterns depend on the relative proportion of alveolar congestion and hemorrhage on one side, and large numbers of neutrophils and fibrinous exudate resulting in collapse of alveolar capillaries on the other (Fig. 38-1). Under the microscope, gram-positive diplococci can be best observed within polymorphonuclear leukocytes (Color Fig. 38-2).

With appropriate therapy, resolution is the usual course of events in pneumococcal pneumonia. This results mainly from the effects of proteases released by macrophages that produce lysis of the intraalveolar exudate followed by its elimination through the airways. Because no destruction of the alveolar framework and capillaries was present, full anatomic and functional restitution is to be expected. However, necrosis and cavitation, including the formation of abscesses, is a rare complication, particularly with

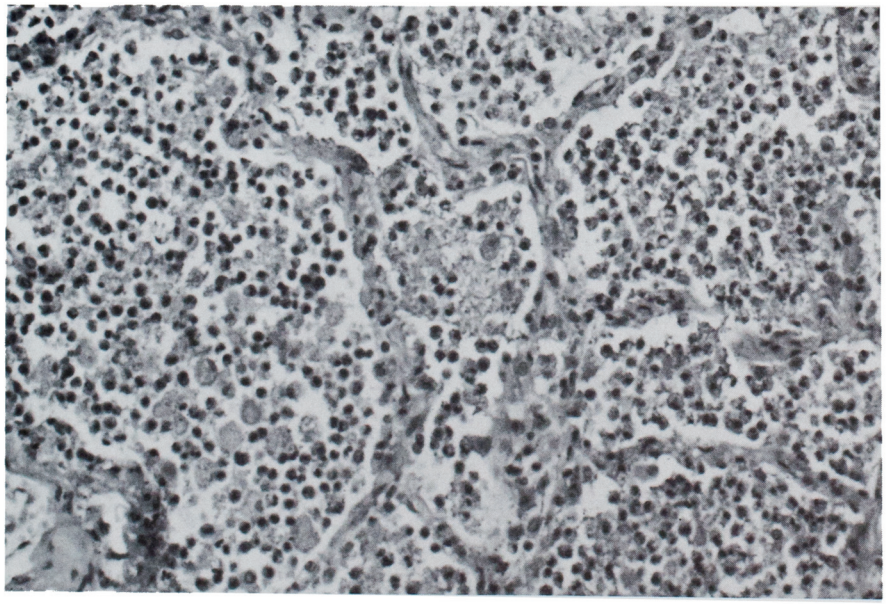

FIGURE 38-1. Histologic features of red hepatization in pneumococcal pneumonia. The alveolar septae are congested but preserved; the alveoli are filled with numerous neutrophils, indicating impending transition to gray hepatization. (H & E stain; low magnification; contributed by the editor.)

certain strains of pneumococcus (*i.e.*, type III). Likewise, failure of the removal of intraalveolar exudate can lead to its organization and subsequent pulmonary fibrosis, which is localized in character. Empyema followed by organization and scarring can result in encasement of the lung in a thick fibrous capsule. Bacteremia with seeding of the infection elsewhere can produce such dreaded complications as bacterial endocarditis, septic arthritis, meningitis, otitis media, and pericardial abscess.[7–9]

Streptococcal Pneumonia

The causative organism is the α- or β-hemolytic streptococcus, but infection more commonly follows invasion of the lung by group A strain β-hemolytic streptococcus. Streptococci are uncommon pulmonary pathogens in the absence of preexisting debilitating disease or systemic infection.[10]

Complete descriptions of streptococcal pneumonia in the absence of antibiotic therapy can be found in casualties of measles outbreaks among military recruits in the early 1900s and during the influenza pandemic of 1918 to 1919.[9,11] More recent descriptions have been made in patients with measles, scarlet fever, and influenza when streptococci became secondary invaders of the lung, most commonly following septicemia.[12]

The clinical syndrome of streptococcal pneumonia typically includes dyspnea, cyanosis, sore throat, hoarseness, sleeplessness, and delirium.[13] In patients with influenza, the clinical course ends in death within 36 hours following demonstrable streptococcal septicemia if antibiotics have not been administered.[14]

The pathologic findings of all stages of β-hemolytic streptococcal pneumonia have been summarized by Spencer.[15] Examination of the thoracic cavity and the lungs usually reveals extensive serosanguineous pleural effusions compressing the lower halves of the lungs, causing their partial collapse. The lungs appear bulky and the surfaces are purple. Dissection may show bronchi full of bloody or purulent fluid and, frequently, extensive parenchymal hemorrhages irregularly distributed throughout.

When the patient survives beyond 4 days without antibiotic treatment, there is rapid necrosis of the alveolar walls that may become quite extensive. Thrombosed capillaries are numerous, and microabscess may develop (Color Fig. 38-3).

In deaths after 1 week of illness, edema is less prominent, the pleura over affected areas becomes covered by thick fibrin, and empyema can often be demonstrated. The cut surfaces reveal frequent abscesses centered on bronchi and bronchioles surrounded by firm areas of parenchymal consolidation with poorly defined peripheral margins.

The microscopic picture is typically one of bronchopneumonia. Damage to bronchial walls is prominent, and the bronchial and bronchiolar epithelia are completely lost. The inflammatory infiltrate extends to the surrounding alveoli (Fig. 38-2). The latter show prominent hyperplasia of type II pneumocytes, edema, and neutrophils. Under extremely high magnification, the short and medium-length chains of gram-positive streptococci can be found with relative ease (Color Fig. 38-4). With healing there is fibrosis around bronchi and along interlobular septa. The extensive tissue damage usually induced by the highly virulent streptococci leads to frequent complications, including abscesses, bronchiectasis, and fibrosis.

Staphylococcal Pneumonia

The staphylococci are a major cause of postinfluenzal bacterial pneumonia among the debilitated, the chronically ill, and the elderly, and they account for about 10% of all bacterial pneumonias.[16] In adults, staphylococcal pneumonia occurs by spread of infection of the upper airways, but it is more commonly the result of hematogenous seeding during staphylococcal bacteremia or septic embolization from a distant site, particularly tricuspid bacterial endocarditis[17] resulting in multiple septic (*i.e.*, bland) infarcts in which the organism can be identified (Color Fig. 38-5; Fig. 38-3). The many antibiotic-resistant strains and the high virulence of staphylococci, particularly *Staphylococcus aureus*, are responsible for the preeminence this organism has recently acquired.

Rarely, fulminant staphylococcal pneumonia in adults can complicate postoperative staphylococcal septicemia. It is characterized by high fever, purulent bloody sputum with numerous

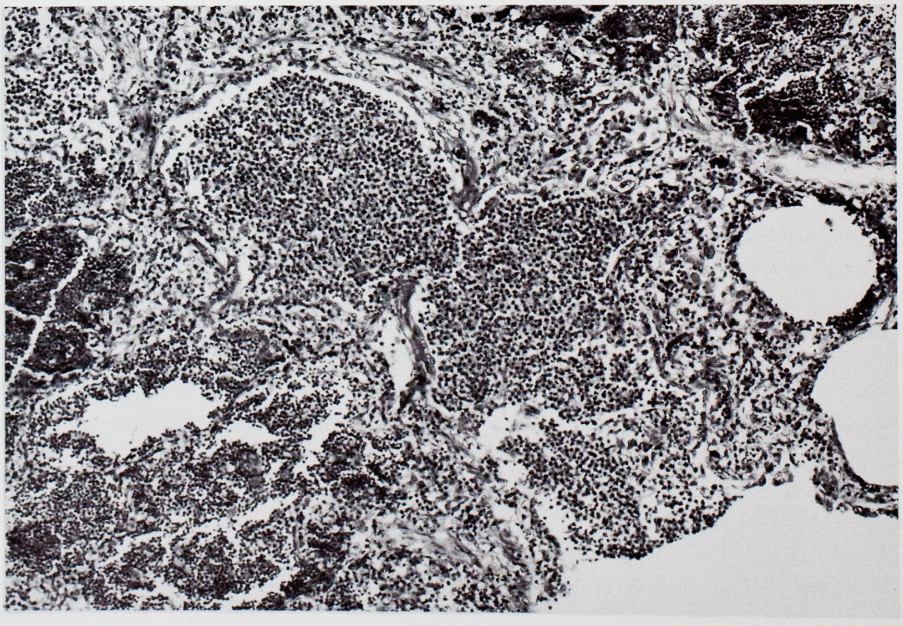

FIGURE 38-2. Bronchiolar abscess with destruction of adjacent alveolar tissue in a patient with β-hemolytic streptococcal pneumonia. (H & E stain; low magnification.) Compare this figure with Color Figure 38-4.

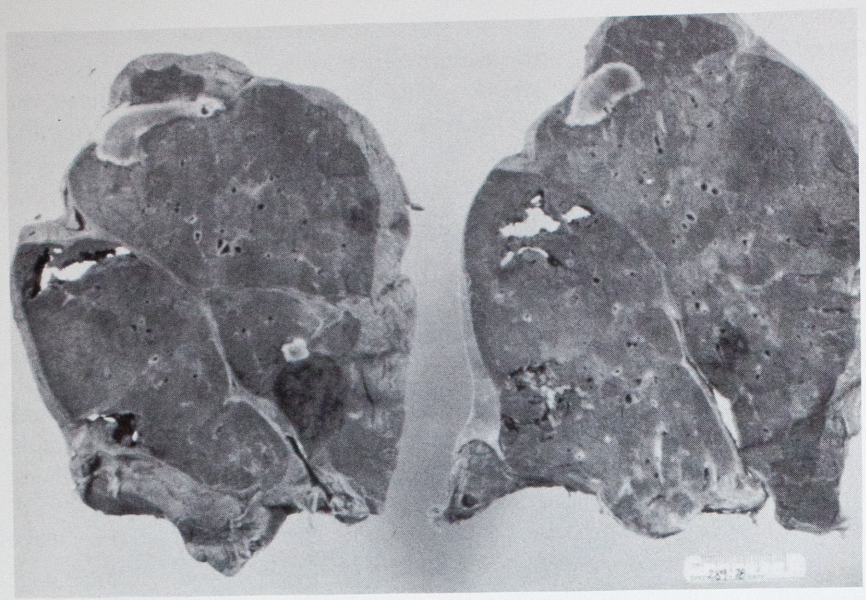

FIGURE 38-3. Characteristic gross appearance of staphylococcal pneumonia secondary to septic emboli from a tricuspid valve infected with *Staphylococcus aureus*. This lung from a young drug addict contains several red and white (bland) infarcts with necrosis of lung tissue. (Contributed by the editor.)

gram-positive staphylococci, and minimal or absent radiologic chest abnormalities.[18]

More commonly, however, staphylococcal pneumonia presents as an acute illness soon after onset of viral infection of the respiratory tract, usually influenza, in a susceptible patient. The clinical illness is usually biphasic, with initial viral symptoms for 4 to 5 days followed by an abrupt clinical deterioration with onset of high fever, chills, cough, and dyspnea. The sputum is purulent and contains abundant leukocytes and many staphylococci. In such cases, the lungs are purple, bulky, and edematous. Pleural reaction may be negligible, but serosanguineous effusions may be present. On sectioning, the bronchi are filled with fluid and the mucosa of the larger bronchi is covered by patches of fibrinous pseudomembranes resembling diphtherial bronchitis. The cut surfaces exude hemorrhagic fluid on gentle pressure, and hemorrhages are widely spread throughout. Parenchymal consolidation is usually inapparent or absent at this early stage.

At a later stage, the lungs demonstrate focal patches of gray-yellow consolidation around bronchi, predominately in the posterior lobe segments. These eventually break down into ill-defined abscesses to connect with small bronchi filled with yellowish, sticky, purulent exudate. The infection spreads outward through the walls of affected bronchi into neighboring air passages and alveoli; abscesses enlarge rapidly and drain into other bronchi. With onset of staphylococcal septicemia, the infection spreads to involve much of the affected lobes and may even turn the entire lung into a honeycombed mass of chronic abscesses (Fig. 38-4).[18] Older abscesses may become lined with granulation and fibrous tissue and with central intracavitary purulent exudate. In such cases, pleural reaction is prominent, with chronic empyema and thick pleural adhesions.

In infants and young children dying of fulminant staphylococcal pneumonia within 2 days of onset of illness, the anatomic pattern is one of lobular or lobar hemorrhagic consolidation and can involve the entire lung. The affected areas are grossly red and collapsed below the surrounding aerated areas; they exude abundant hemorrhagic frothy fluid. Microscopically, the alveoli are filled with blood, edema, occasional macrophages, few polymorphonuclear leukocytes, and numerous large, gram-positive staphylococci. The bronchi are filled with purulent exudate and show extensive damage of the mucosal lining. There is little pleural reaction.

Staphylococcal pneumonia of a less fulminant course in children is characterized by gray-yellow patches of alveolar consolidation bulging on the pleural surface and covered by a well-formed fibrin layer. Empyema is a common complication. Sectioning of the lungs reveals many areas of consolidation broken down into abscess cavities that are more numerous in children with longer survival (Color Fig. 38-6). Pneumatoceles can occur secondary to the destruction of alveolar tissue where air becomes entrapped by a valvelike obstruction of unsupported airways. Air cavities form

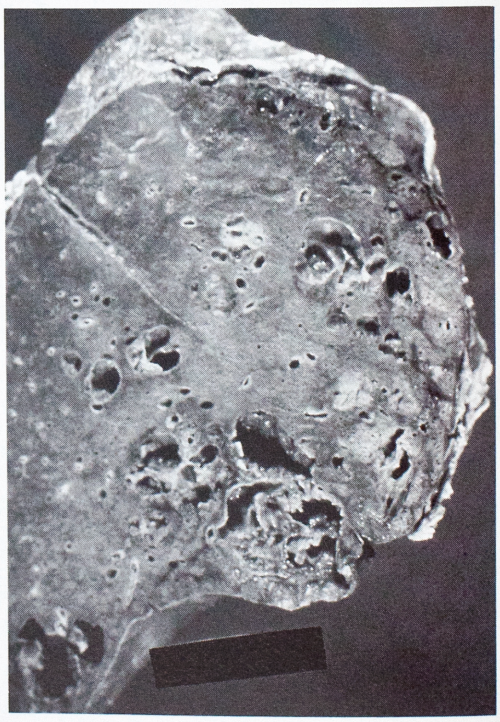

FIGURE 38-4. Gross appearance of the lung in an adult with staphylococcal pneumonia. There is massive replacement of the lung parenchyma by pneumonic consolidation and numerous abscesses. The pleura is thickened by fibrinopurulent exudate. (Contributed by the editor.)

and can enlarge substantially to be recognized on chest x-ray films or at autopsy. Ruptured pneumatoceles cause pneumothorax and pyopneumothorax to further complicate the clinical picture. With resolution of the pneumonia, they can resolve spontaneously as the excessive intracystic pressure dissipates through the reestablished collateral ventilation.[18] In young infants and neonates, fulminant pneumonia with hyaline membranes can lead to death within 48 hours of onset (Color Fig. 38-7).

Diphtherial Pneumonia

Diphtheroids comprise a wide variety of corynebacteria, including the JK group of corynebacteria.[19] They are non–spore-forming gram-positive bacilli of great diversity forming part of the normal flora of the skin and mucosal membranes of humans. They range from 0.5 μm to 1 μm in diameter by several micrometers in length. One case of culture-proven diphtherial pneumonia has been characterized histologically.[19] The patient was profoundly neutropenic as a result of chemotherapy for acute myelogenous leukemia. Pneumonic presentation was characterized by pleuritic chest pain, hypoxemia, hemoptysis, and rapidly worsening bilateral patchy pulmonary infiltrates. Blood and urine cultures yielded gram-positive bacilli after 4 days that were resistant to multiple antibiotics. The patient died shortly thereafter.

Autopsy revealed markedly congested edematous lungs with deep red cut surfaces exuding bloody fluid and with numerous areas of tan-white consolidation. Microscopically, the lungs were markedly congested with numerous intraalveolar hemorrhages. Near the areas of consolidation, gram-positive bacilli were seen growing along alveolar walls in great numbers without inflammatory response, presumably because of the patient's neutropenia. Many alveoli were nearly filled with microorganisms and showed extensive necrosis of the alveolar epithelial lining, and in the most consolidated areas the alveolar walls were completely disintegrated. A pure culture of the organism was recovered from lung tissue obtained at autopsy within 24 hours of plating on sheep blood agar under aerobic conditions.

GRAM-NEGATIVE PNEUMONIAS

Haemophilus influenzae *Pneumonia*

This is an unusual form of pneumonia in adults.[20–24] The microorganism may be isolated from sputum and throat cultures, but the detection of *H. influenzae* from these sources does not necessarily mean it is the cause of the pneumonia. Because great difficulty exists in separating pathogenetic from harmless colonization by *H. influenzae*, specific criteria have been developed in an attempt to solve such a dilemma. In principle, if isolation of *H. influenzae* is from blood, pleural fluid, or lung tissue, a pathogenetic role of this microorganism is favored.

H. influenzae pneumonia appears to be more common in specific settings, such as in patients with chronic pulmonary disease and alcoholism. Clinically, as with other types of pneumonias, fever, cough, chills, and pleuritic pain appear to be the most prominent symptoms. Histologically, an acute inflammatory reaction similar to that observed in other pneumonias is found with destruction of mucosa and bronchial walls. In some cases, an abscess may develop. The microorganisms may be difficult to identify and appear as small pleomorphic bacilli (Color Fig. 38-8).

The pathogenetic properties of *H. influenzae* are determined by the presence of a polysaccharide capsule. Six types (*i.e.*, A to F) have been described. However, unencapsulated strains, which are nontypable, appear to be associated with chronic bronchitis, but they apparently rarely invade the bloodstream. In cases in which typable strains are isolated, types B and F are more frequent.[25] The advantage of having this information is crucial, because it is usually a capsulated or typable strain that produces bacteremia. In addition, the finding of a typable strain in the setting of radiographic evidence of pneumonia speaks in favor of its being a pathogen.

The clinical course of *H. influenzae* pneumonia will depend on the conditions of the host and on early treatment. Otherwise, it may go on to develop abscesses, dissemination, and death.

Serratia *Pneumonia*

Serratia marcescens is an aerobic, motile bacillus belonging to the family Enterobacteriaceae, and it is not a common cause of pneumonia.[26] In the past, *S. marcescens* was considered a nonpathogen saprophyte. However, Yu and colleagues, between 1968 and 1977, reported a series of 76 cases in one hospital alone.[27] Goldstein and associates reported 16 cases, all of them autopsy-cultured, proven cases of *S. marcescens* as a sole organism.[28] Underlying conditions such as malignant processes, renal failure, or liver disease have been associated with this organism. Sources of outbreaks have been traced to different paths, including hand lotions, disinfectants, and intravenous solutions.[26] Cross-contamination of patients by hospital personnel appears to be the most important mechanism of transmission.[26] Although its incidence is variable, it may represent as much as 17% of nosocomial pneumonias.[29]

Grossly, patchy areas of consolidation and focal hemorrhages, more extensive in the lower lobes and usually bilateral, appear to be characteristics. Microscopically, an acute, necrotizing process is present with formation of microabscesses. Vasculitis of both arteries and veins may be seen. However, these histopathologic changes are not pathognomonic of *S. marcescens*. In neutropenic patients, the histologic picture may be that of neutropenic pneumonia.

In a more recent description, *Serratia plymuthica* pneumonia was found in an immunocompromised patient.[30] The organism was cultured from the sputum, but its origin was not clear; however, this organism has been isolated from fresh water.[31] Treatment with antimicrobials is necessary; otherwise, the illness may progress to septicemia and death.

Pseudomonas aeruginosa *Pneumonia*

Pseudomonas aeruginosa pneumonia appears to be associated with underlying conditions such as malignant neoplasms or other conditions that impair host defenses.[32–34] Because of its high mortality and difficulty in treatment, it is imperative to recognize this organism. At the same time, it is a common colonizer of the oropharynx in patients treated with broad-spectrum antibiotics as well as in the presence of chronic lung and heart disease.[35] Therefore, the presence of *P. aeruginosa* in sputum has limited diagnostic significance. In the presence of radiologic findings of pneumonia and the recovery of the organism from lung, pleural fluid, or blood, the pathologist can arrive at an unequivocal interpretation. *P. aeruginosa* pneumonia has been recognized as a cause of infection in

burned patients as well as from contamination through medical equipment.[36–39]

Rose and colleagues, in their study of 801 patients with pneumonia, found that 59 (7.4%) cases were caused by gram-negative bacilli.[34] Of those, 19 cases were caused by *P. aeruginosa*. Seventeen of these 19 patients acquired their infection while in the hospital, and only two patients had the infection at the time of admission. Although the infection appeared as a terminal event in 18 cases, 1 case followed a protracted course of more than 90 days. As expected, the pneumonia was more fulminant when associated with bacteremia.

The gross characteristic lesions of *P. aeruginosa* include poorly defined hemorrhagic nodules (Color Fig. 38-9); sometimes the nodules are umbilicated. No specific lobe is more commonly affected. Microscopically, there is extensive necrosis with areas of hemorrhage. A characteristic feature is the presence of vasculitis involving small arteries and veins (Color Fig. 38-10). Gram stains will reveal the presence of numerous bacilli in the vascular wall (Color Fig. 38-11). The paucity of inflammatory cells is due to the secretion of a toxin by the organism that destroys neutrophils. In some cases, *P. aeruginosa*, for unknown reasons, adopts a filamentous morphology that may confuse the observer (Color Fig. 38-12).

The course of this infection is also dependent on the underlying disease, and the mortality is high.

Klebsiella pneumoniae *Pneumonia*

Also known as Friedländer pneumonia,[40–42] *Klebsiella pneumoniae* infection is most often seen in hospitalized, alcoholic, and diabetic patients, as well as in individuals with poor oral hygiene. It has been suggested that in nursing homes about 40% of cases of pneumonia are caused by this organism.

Clinically, the patient presents as febrile and cyanotic, and the infection may appear as either acute or chronic. Chest radiographs may show bilateral pulmonary multifocal consolidations or cavitation. However, clinically or radiologically it is indistinguishable from other types of pneumonia.

Grossly, areas of hemorrhage, necrosis with mucoid appearance, and abscess formation may be observed (Color Fig. 38-13). Microscopically, there is extensive intraalveolar exudate with predominance of neutrophils and macrophages. Gram stains demonstrate the presence of numerous bacilli (Color Fig. 38-14). In the presence of chronic infections, the finding of fibrosis is more characteristic, as is the scant number of bacilli demonstrable by special stains.

Escherichia coli *Pneumonia*

Escherichia coli pneumonia is unusual and likely to follow a genitourinary or gastrointestinal infection.[43] Clinically and radiologically, this type of pneumonia does not have specific features and may not be distinguishable from other more common types of pneumonias. Once established, it may follow an aggressive course with a mortality as high as 40%.

Microscopically, it is characterized by an inflammatory exudate rich in fibrin, a predominance of neutrophils and macrophages, and sparing of the bronchial mucosa and bronchioles. Gram stains will show the presence of the bacillus (Color Fig. 38-15).

Bordetella pertussis *Pneumonia* (Whooping Cough)

Bordetella pertussis rarely causes fatal illness. A detailed description of this pneumonia appeared before the mid-forties, and the most comprehensive series was compiled by Feyter from 225 deaths of patients with whooping cough in the late twenties, as reviewed and summarized by Spencer.[44]

Pulmonary reaction is characteristically an endobronchitis or endobronchiolitis that progresses to peribronchitis and interstitial pneumonia. The bronchial mucosa is initially edematous with early acute inflammation, rapidly followed by mucopurulent fluid filling the smaller bronchi and bronchioles. If the infection worsens, the mucosa develops multiple shallow ulcerations as irregular areas of the bronchial epithelium become necrotic and are shed. The walls of bronchi, bronchioli, and alveoli become infiltrated by a prominent population of mononuclear cells consisting mostly of lymphocytes and plasma cells. The histologic picture can resemble adenovirus infection. Gram stain reveals short gram-negative coccobacilli that resemble *H. influenzae*.

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