Infectious Pneumonias: A Review

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Diplococcus pneumoniae remains the most frequent cause of community-acquired bacterial pneumonia. Other frequently isolated bacterial pathogens are *Hemophilus influenzae, Klebsiella* organisms, and *Staphylococcus aureus.* The etiologic agents most commonly implicated in hospital-acquired pneumonias are gram-negative bacilli including *E. coli, Proteus* organisms, and species of *Klebsiella-Enterobacter, Pseudomonas,* and *Serratia.*

Among older children and young adults, *Mycoplasma pneumoniae* is a common cause of pneumonia. Influenza is the most important cause of viral pneumonia in adults, but there is increasing concern about pulmonary infection due to adenoviruses. In those with a history of travel to endemic areas, the diagnosis of fungal pneumonia due to *Histoplasma capsulatum, Blastomyces dermatitides,* or *Coccidioides immitis,* should be considered. Pneumonias due to opportunistic fungi (including species of Candida, Aspergillus, and Phycomycetes) and higher bacteria such as *Nocardia asteroides* are also on the increase, and these arise mostly in compromised hosts.

Treatment of pneumonia almost always must be started before culture results are known and in the overwhelming majority of cases, appropriate regimens can be selected after taking an adequate history, doing a careful physical examination, evaluating expectorated sputum for cells and organisms, and examining the chest x-ray. Although anti-infective agents are the mainstay of treatment for most infectious pneumonias, supportive therapy, including adequate tracheobronchial toilet, drainage of abscesses, oxygen inhalation, maintenance of adequate nutrition, and monitoring for superinfection and anti-infective side effects may be life-saving in certain situations.

Webster's dictionary defines the Greek-derived term pneumonia as "disease of the lungs characterized by inflammation and consolidation, followed by resolution." Pneumonia can occur secondary to a myriad of etiologies, including infections, tumors, vasculitis, chemicals, toxins, or radiation.

The purpose of this article is to discuss the various common and uncommon infectious pneumonias, their diagnosis, and management.

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Types of Infectious Pneumonias

Bacterial

Pneumococcal

In the pre-antibiotic era, 95 to 98 percent of pneumonia in hospitalized adults was attributed to the pneumococcus. Presently, although the percentage has fallen, *Streptococcus pneumoniae* is still the most common pathogen causing bacterial pneumonia. There are more than 80 capsular serotypes of the pneumococcus as demonstrated by Neufeld's reaction.[1]

In a previously healthy adult, the classical attack of lobar pneumonia due to the pneumococcus is often preceded by an upper respiratory tract infection, and the onset of the lower respiratory tract manifestations is usually abrupt. About 80 percent have a single shaking chill – multiple rigors suggesting demonstrable bacteremia. Cough productive of purulent sputum, dizziness, and pleuritic chest pain are present in 75 percent of cases. Physical examination will reveal findings of consolidation in the majority of cases, and this is usually confirmed by x-ray examination. Although the white blood cell count is usually elevated, it remains below 10,000 cells/mm^3 in at least 25 percent of cases of uncomplicated pneumococcal pneumonia. Consequently, the diagnosis must not be discarded on the basis of a normal peripheral white blood cell count. Upon treatment, improvement usually occurs within 12 to 36 hours, although the temperature may persist for longer than four days. Pneumococcal pneumonia in the elderly or debilitated may present more insidiously, the major manifestations being mental obtundation, congestive heart failure, or marked prostration. In such cases, fever may not be present, or the temperature may be only slightly elevated.

Austrian and Gold found that nearly three-fifths of all deaths from pneumococcal pneumonia and bacteremia, in the absence of an extrapulmonary focus of infection, resulted from types I, III, IV, VII, VIII, or XII in persons 50 years of age or older, or in those with complicating illnesses. Other factors adversely affecting prognosis are multilobar involvement, the presence of extrapulmonary suppurative complications and leukopenia (< 3,000 WBC/mm^3).[1]

Alcoholism is the most common predisposing factor in the acquisition of pneumococcal pneumonia. Alcohol has been shown to impair glottis closure, reduce leukocyte adherence, impair macrophage phagocytosis and/or killing, and delay leukocyte mobilization. Additionally, patients with alcoholic liver disease may have circulating inhibitors of chemotaxis. Then too, malnutrition is commonly associated with alcoholism and this results in multivitamin deficiency, the most common of which is folate deficiency, and this in turn may result in leukopenia.[2-12]

Those with sickle cell disease also appear more susceptible to severe pneumococcal disease.

Klebsiella

Klebsiella pneumoniae is an encapsulated, nonmotile, gram-negative rod. There are at least 100 serotypes of *Klebsiella pneumoniae* identifiable by various techniques. The lower serotypes (1 to 6) are most frequently associated with non-hospital-acquired lower respiratory tract disease, although other types have been implicated. The lower serotypes have in the past been included under the diagnosis of Friedlander's pneumonia.

Acute pulmonary infection, especially among alcoholics and debilitated patients, usually results in serious disease with a substantial mortality rate, especially if inappropriately treated. Bacteremia occurs in about 30 percent of cases. The acute pneumonia, which may be due to aspiration, is usually in the upper lobes, especially the right, and bulging of the fissure is common (Figure 1).

Subacute, or even chronic, disease occurs rarely. Friedlander's bacillus is no respecter of lobar boundaries and the subacute form is also characterized by abscess formation and substantial anemia.[13-19]

The previously over-emphasized "currant-jelly" appearance of sputum from these patients occurs in a minority of cases and is not exclusive for *Klebsiella* infection, having been reported in other bacterial pneumonias, notably that due to pneumococcus types III and VIII. Thin sputum may also be found.

Hemophilus influenzae

H. influenzae or Pfeiffer's bacillus is an aerobic, gram-negative coccobacillus frequently found in the respiratory tract of children and adults. It is a common pathogen in children, especially among those below five years of age.

Hemophilus influenzae infection in adults has been associated with underlying disease that undermines host-defense mechanisms, namely alcoholism, diabetes mellitus, chronic bronchopulmonary disorders, hypogammaglobulinemia, dysgammaglobulinemia, and antecedent viral respiratory disease. Recent reports, however, show an increasing incidence of *H. influenzae* infections in the previously healthy adult, the postulated reason being that with the widespread use of antibiotics during childhood, suppression of protective anticapsular antibody formation occurs and this increases susceptibility to *H. influenzae* infections in later years. In a study of sera from 29 normal adults, Norden, Callerame, and Baum demonstrated that two-thirds lacked bactericidal activity, but more recent studies using more sensitive techniques suggest this may not be the explanation.[20-24]

There are six *H. influenzae* types, namely A, B, C, D, E, and F, but Type B has been most frequently implicated in serious infections due to this organism. Type F is next in frequency.

Lobar pneumonia secondary to *H. influenzae* infection may resemble lobar pneumococcal pneumonia (Figure 2). Complicating empyema, abscess formation, or pleural fibrosis may occur.

Staphylococcus

There are two types of staphylococcal pneumonia, (1) that arising from the upper respiratory tract (primary) and (2) that occurring as a consequence of hematogenous spread. Only a small percentage of upper respiratory tract acquired pneumonias are due to *S. aureus*, but this organism is the leading cause of embolic pneumonia. It is important to stress that the skin lesion responsible for embolic staphylococcal pneumonia may be surprisingly small and appear innocuous.

Upper respiratory tract-acquired staphylococcal pneumonia frequently follows virus influenza. There are two distinct clinical syndromes. In some cases the staphylococcus invades 2 to 30 days after the virus infection, but there is no evidence of virus in the lung itself and the prognosis is good if the infection is treated with appropriate antibiotics. In other cases the staphylococcus and the influenza virus both invade the lung parenchyma; when this happens mortality rates are high even if the staphylococcal infection is treated promptly.[25,26]

Primary staphylococcal pneumonia also complicates pulmonary tuberculosis; indeed, if staphylococcal pneumonia occurs when there is no influenza virus in the community, a careful search must be made for tubercle bacilli. Those with chronic lung disease, pulmonary cancer, and those treated with antimicrobials may also suffer from primary staphylococcal pneumonia. The onset is usually abrupt with chills, high fever, cough productive of purulent sputum, and pleuritic chest pain. Leukocytosis is common but bacteremia is infrequent. In patients with underlying chronic debilitating disease or compromised immune function, the onset is often more insidious, but the patient is nevertheless toxic. In those with combined influenza virus-staphylococcal pneumonia, a normal white blood count or leukopenia is characteristic; the more severe the leukopenia, the worse the prognosis.

In primary staphylococcal pneumonia among infants and young children, complicating pyopneumothorax and pneumatocele formation occur early.

The onset of clinical disease is often not as dramatic in secondary staphylococcal pneumonia arising hematogenously from a non-pulmonary focus of infection. This is exemplified by the patient whose chest x-ray is shown in Figure 3. The patient was a young male drug abuser who entered the hospital because of fever and weight loss. As is often the case, there was little evidence of toxicity and physical examination did not show consolidation; chest x-rays showed multiple, patchy, rounded densities. In such cases a gradual clinical response to therapy is the rule, but the course is often stormy and occasionally death may occur in spite of appropriate antibiotics. The addict with metastatic staphylococcal pneumonia frequently has right-sided staphylococcal endocarditis as well.

Streptococcal

The incidence of pneumonia secondary to group A hemolytic streptococcus is not as great now as during the pre-antibiotic era. It may occur as a complication of an antecedent viral influenza or may complicate underlying chronic lung disease. Empyema is found frequently, with early effusion, often serosanguinous, characterizing the disease. Bacteremia occurs in 10 to 15 percent of cases.

Anaerobes

Necrotizing pneumonitis, with abscess formation, is characteristic of anaerobic disease of the lung. If a patient enters the hospital with an abscess cavity on chest x-ray and a foul smelling sputum, the diagnosis is almost certainly anaerobic disease, caused for the most part by bacteroides species and anaerobic strepto-

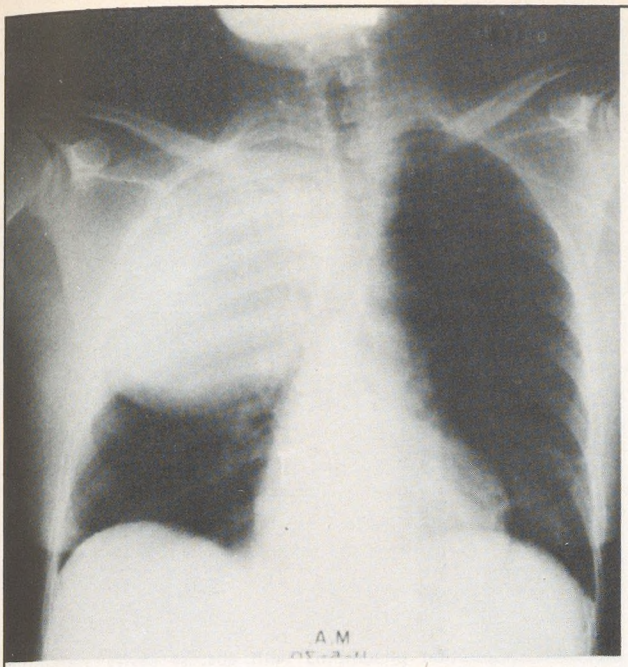

Figure 1. A dense infiltrate with bulging of the minor fissure is noted in this chest radiograph of a patient with acute *Klebsiella* pneumonia involving the right upper lobe.

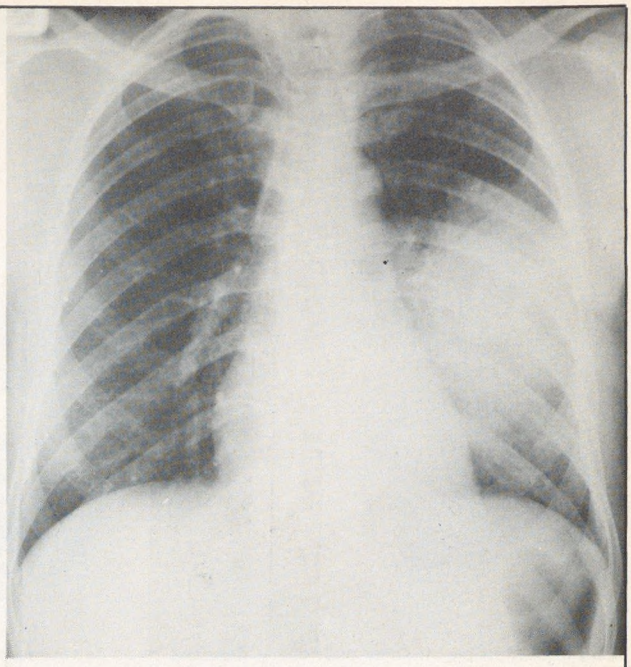

Figure 2. Lobar pneumonia secondary to *Hemophilus influenzae* pneumonia may resemble lobar pneumococcal pneumonia. This is a radiograph of a patient with *Hemophilus influenzae* pneumonia showing dense infiltrate at the left mid-lung field.

cocci (Figure 4).

Anaerobic bacteria are normally found on the skin, and in the mouth, gastrointestinal tract, and female genitourinary tract. Pulmonary infection can occur after aspiration of mouth contents or by hematogenous spread during anaerobic bacteremias, especially after colon or genitourinary tract manipulation, or following septic abortion. Among heavy alcohol imbibers, especially those with bad teeth, aspiration plays a major role, especially if there are episodes of loss of consciousness. Not infrequently, the infiltrates are found in the dependent pulmonary segments (typically the posterior segments of the upper lobes and the superior segments of the lower lobes). Clubbing of the fingers and toes occurs in many of those with putrid lung abscesses.[27-30]

Other Gram-Negatives

The etiologic agents most commonly implicated in hospital-acquired pneumonias are the enteric gram-negative bacilli such as *E. coli* and strains of *Proteus, Klebsiella* and *Enterobacter*. Other gram-negative organisms involved are strains of *Pseudomonas* and *Serratia*.

Factors predisposing to hospital acquired gram-negative pneumonia include the use of contaminated inhalation therapy equipment, aspiration in comatose or debilitated patients with poor cough or gag reflex, use of unsterile tracheal suctioning techniques, and antibiotic use and/or abuse. Additionally, bacteremias may occur from extrapulmonary sites of infection, such as the genitourinary tract, gastrointestinal tract, or decubitus ulcers, and this may be followed by pneumonia. Gram-negative pneumonia may also be community acquired especially in middle-aged men suffering from alcoholism or diabetes; occasionally such pneumonias follow viral influenza.[16,17,31]

Pneumonias due to *E. coli* are thought to be manifested by patchy bilateral lower lobe infiltrates; empyema may occur early in the course of the infection. Cavitary lesions are common with *Pseudomonas* pneumonias (Figure 5).[32,33] *Proteus* and *Klebsiella-Enterobacter* infections produce dense lobar consolidations, sometimes with abscess formation. In a study of characteristics of *Serratia* pneumonias, Meltz and Grieco noted that the absence of cavity formation helps differentiate *Serratia* pneumonias from that caused by *Pseudomonas*.[34] However, these differences in clinical pattern among gram-negative pneumonias are based on small numbers of cases and the differences may be over-emphasized.

Non-bacterial Infectious Pneumonias

Mycoplasma

Mycoplasma pneumoniae is a common cause of pneumonia among older children and young adults, especially among military recruits.[35]

The characteristic features of pneumonia due to this agent are fever, severe headache, a dry hacking cough, and a paucity of chest findings on physical examination despite extensive pulmonary infiltrates which may be found on x-ray examination (Figure 6). On occasion there may be severe

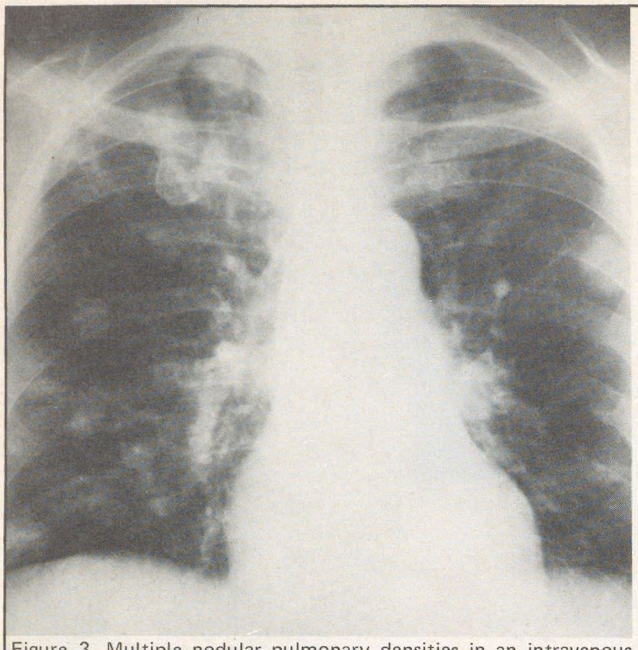

Figure 3. Multiple nodular pulmonary densities in an intravenous drug abuser with acute staphylococcal endocarditis and septic emboli to the lungs.

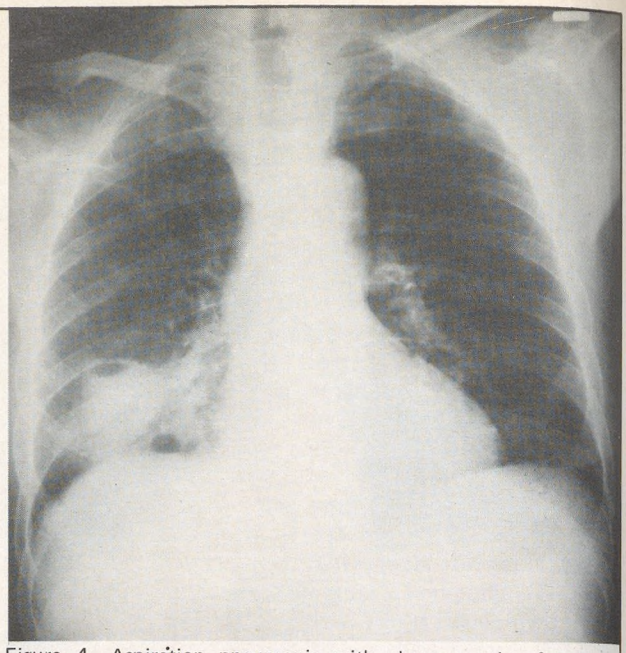

Figure 4. Aspiration pneumonia with abscess cavity formation involving the right middle lobe.

rigors and/or striking pleuritic pain. Up to one third of cases may have non-specific ear complaints and ear examination may reveal bullous or hemorrhagic myringitis. Pneumonia due to *Mycoplasma* is almost always self-limited, but it is important to stress that the disease may be serious and life-threatening. *Mycoplasma* infection is particularly severe in those suffering from sickle cell anemia. Cold agglutinin elevation occurs in at least two thirds of cases; if titers are high enough, hemolytic anemia may supervene. The white blood cell count is usually normal or slightly low, but may be elevated after the first week of disease. Abscess formation and pleural effusion have been reported as complications. Antimicrobial therapy, although effective in improving clinical signs and symptoms, may not eradicate the organism from the respiratory tract; throat cultures are often positive long after clinical recovery has ensued. In patients with high titers of cold agglutinins and consequent hemolytic anemia, it is important to warm bottles of blood before transfusion, lest local thrombosis supervene. An increasingly frequently reported complication of *M. pneumoniae* infection is meningoencephalitis.[36]

Viruses

Among the viruses causing pneumonia in adults, the most important are influenza A and B whose incidence peaks during the winter. Those most susceptible to both severe influenza virus pneumonia and combined viral-bacterial pneumonia are the very old and those with underlying cardiopulmonary disease. Influenza virus pneumonia ranges in extent from lobular limited disease to massive bilateral infiltrates associated with severe hypoxia and a grim prognosis.[37-40]

Adenoviral pneumonia is more commonly found among young adults, especially among military recruits.[41]

Pneumonia occurs in adults with varicella more frequently than in young children with this disease. Krugman reported 33 percent occurrence in the adult.[42] Characteristically, x-rays show multiple nodular or interstitial infiltrates. In most cases, despite extensive x-ray infiltrates and what appears to be overwhelming illness, recovery occurs after several days of profound illness. In this regard, varicella pneumonia differs markedly from diffuse influenza virus pneumonia. Following varicella pneumonia, lung calcification may be found.

Cytomegalovirus pneumonia in the infant may be primary or secondary to disseminated disease. In the adult, there is almost always a severe underlying disease that compromises immune defense mechanisms, ie, leukemia, Hodgkin's disease, lymphosarcoma, etc.[37,40,43]

The agents that cause most viral pneumonias in children are influenza A and B, parainfluenza (1 to 4), respiratory syncitial virus, adenovirus, and measles.

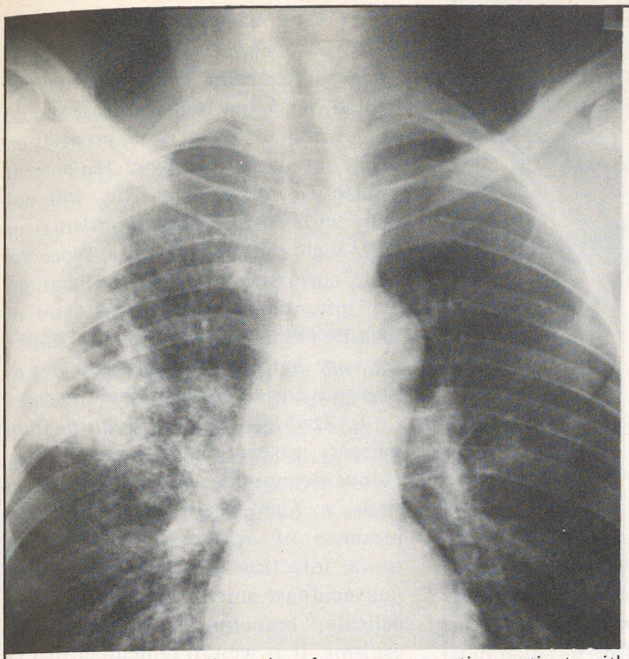

Figure 5. Chest radiograph of a post-operative patient with necrotizing pneumonia of the right upper lobe secondary to *Pseudomonas.* The patient was on intermittent positive pressure breathing (IPPB) therapy.

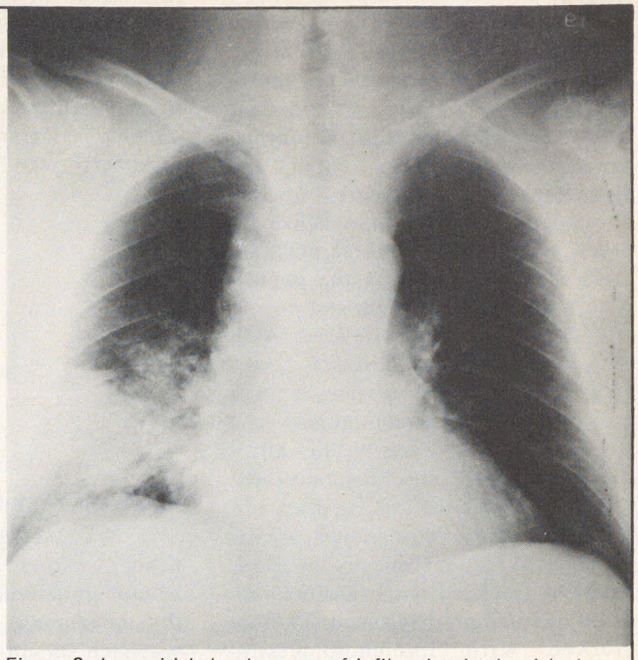

Figure 6. Interstitial-alveolar type of infiltration in the right lower lobe of a patient with *Mycoplasma* pneumonia. The patient had only a few fine rales at the right lung base.

Q-Fever

Q-Fever is a rickettsial disease caused by *Rickettsia burnetti.* For man, domestic animals are the main source of contamination, and pneumonia is most frequent among breeders, veterinarians, butchers, slaughterhouse workers, and laboratory personnel.[44]

Clinically, the disease may be difficult to differentiate from pneumococcal pneumonia, *Mycoplasma* infections, or ornithosis. The sputum smear may help in that polymorphonuclear leukocytes are almost always absent.

Ornithosis

The agent of ornithosis or psittacosis is an obligate, intracellular parasite containing both RNA and DNA. Bird droppings carry the agent and infection takes place by inhalation of infective dust. Man-to-man transmission is rare. The disease may be difficult to differentiate from bacterial pneumonia. Headache is a common feature and pleural pain occurs in at least 25 percent of cases. Splenomegaly is found in up to 25 percent of cases. As with Q-fever, the sputum ordinarily contains only scant numbers of polymorphonuclear leukocytes.[45]

Pulmonary Tuberculosis

Pulmonary tuberculosis, in the acute pneumonic form, is found mostly in the elderly and among those with deficiencies in delayed immune mechanisms. In some cases a tuberculous hilar node ruptures into a bronchus with consequent pneumonia in the associated lobe or segment. It is well to remember that lobular or lobar pneumonia can occur in young adults and may involve the lower lobes, and the duration of clinical illness, at the time the physician first sees the patient may be brief. Sputum smears may show many polymorphonuclear leukocytes or very few. In cases of tuberculous pneumonia, sputum examination usually shows many acid-fast bacilli, but sometimes it may be extremely difficult to find the organisms; in such cases, bronchoscopic washings are usually positive.

Fungi

In patients with a history of travel to or residence in endemic areas, the diagnosis of fungal pneumonia should be considered, bearing in mind that a considerable period of time may elapse between exposure and onset of clinical illness. Thus, for example, we have seen acute coccidioidal pneumonia, accompanied by erythema nodosum, one year after a young woman left the endemic area.

Histoplasma capsulatum is endemic in the eastern and midwestern United

States. Infection occurs by inhalation of fungi in dust and soil. *Blastomyces dermatitides* is endemic in the southeastern United States. *Coccidioides immitis* is endemic in California, Nevada, Arizona, Texas, Utah, and New Mexico. The acute, uncomplicated, atypical, pneumonia-like illnesses caused by these three fungi are fairly common events in the population, are generally benign, and do not require chemotherapy. However, with each of these fungal diseases, severe progressive or chronic disease, at times associated with extrapulmonary dissemination, may occur. In histoplasmosis and coccidioidomycosis, systemic dissemination appears to occur more frequently among patients with lymphatic malignancy or other diseases associated with defects in delayed immune mechanisms or in those treated with immunosuppressive agents.

There are three major clinical forms of actinomycosis: cervicofacial, abdominal, and thoracic. Pulmonary infection is characterized by formation of abscesses, chest wall fistulas, and chronic draining sinuses.[46]

On the other hand, nocardial, aspergillus and phycomycete *(Mucor, Absidia, Rhizopus)* pneumonias arise mostly in compromised hosts, particularly those with leukemia, lymphoma, carcinoma, or organ transplants, who because of their disease, chemotherapy, or immunosuppressive therapy, have impaired defense mechanisms. With nocardial infections the defects are in delayed immunity, whereas in aspergillus and *Mucor* infections, the defects relate primarily to polymorphonuclear leukocyte function. Phycomycetes and aspergilli grow into blood vessels so that each tends to present as pulmonary infarction with hemoptysis.[43,47] Recent data also indicate that in patients with leukemia these fungi can cause a pneumonic infiltrate, in which a typical fungus ball appears. In such cases, the fungus ball has the same malignant implications as do aspergillus or *Mucor* pneumonias. This is in striking contrast to fungus balls arising in established cysts or cavities. Ordinarily this type of fungus ball is benign. *Candida* pneumonia has been thought to be extraordinarily rare. Clearly this is not so. In the severely compromised host, particularly one receiving antibiotics and suffering from severe leukopenia, *Candida* pneumonia may supervene. In most cases diffuse lower lobe infiltrates characterize the disease, but lobular infiltrates may be seen. Rarely, *Candida* pneumonia occurs in an apparently healthy individual.

Diagnostic Work-Up

1. *Gram's stain* – A carefully done Gram's stain of sputum can be most helpful in determining the etiology of the pneumonia. The ideal sputum specimen should be free of squamous cells which indicate contamination with oropharyngeal secretions. The presence of polymorphonuclear leukocytes and/or alveolar macrophages indicates that the sputum specimen has come from the lower respiratory tract.

If polymorphonuclear leukocytes predominate in the sputum Gram's stain, this suggests a bacterial etiology, but predominance of polymorphonuclear leukocytes may also be seen in some cases of mycoplasmal and adenoviral pneumonia, and in tuberculosis.[48]

It is crucial that proper decolorization of the stain be done, since gram-negative organisms may appear gram-positive in underdecolorized specimens. The polymorphonuclear leukocytes in a properly decolorized Gram's smear should stain pink. If proper decolorization is not achieved, *Klebsiella* may be mistaken for pneumococci with disastrous consequences for the patient. In some cases *Klebsiella pneumoniae* may appear as a pleomorphic gram-variable organism even if the Gram's stain is adequately decolorized (Figure 7).

2. *Cultures* – Care must be taken that the sputum specimens for culture be sent to the laboratory and plated out immediately; some organisms such as pneumococci may autolyze, if not processed promptly. Sputum specimens are inadequate for anaerobic cultures because of unavoidable contamination from anaerobic mouth flora; as a matter of fact, there are more anaerobes than aerobes in the upper respiratory tract.

3. *Potassium hydroxide (KOH) smear* – Sputum from patients suspected of having fungal disease should be examined in a wet preparation using one or two drops of ten percent potassium hydroxide. This will not help with *Histoplasma capsulatum* or with higher bacteria such as *Nocardia* and, surprisingly, KOH preparations are infrequently positive in cases of invasive aspergillosis, but the smears are very helpful in suspected cases of blastomycosis or coccidioidomycosis.

4. *Acid-fast stain* – Sputum from patients suspected of having tuberculous pneumonia should be examined with a Ziehl-Neelsen stain for the presence of acid-fast bacilli. If *Nocardia* infection is suspected, a modified acid-fast smear may demonstrate delicate, branching, filamentous organisms. It is well to remember that in tuberculous pneumonia several smears may be negative and then inexplicably a smear may show a myriad of tubercle bacilli.

5. *Serologic studies* – These are now available for the diagnosis of toxoplasmosis, cytomegalovirus disease, or fungal infections such as *Candida, Aspergillus,* or *Cryptococcus.*

The definitive diagnosis of Q-fever and ornithosis is ordinarily made by demonstration of at least a four-fold rise in serum antibody titers.

6. *Transtracheal aspiration* – If for some reason satisfactory sputum cannot be obtained, careful transtracheal aspiration may be done bearing in mind the potential complications of such a procedure (Table 1). This is by no means an innocuous procedure and should be undertaken only after careful consideration.[49-51] In many patients a careful fiberoptic bronchoscopy with multiple-lumen technique may be an alternative approach, even though the likelihood of contamination is greater than with transtracheal puncture.

7. *Lung biopsy* – For diagnosis of obscure pulmonary infiltrates in compromised hosts, a lung biopsy, with histopathologic examination after proper staining of the specimen, may be necessary to demonstrate the etiologic agent. Some recommend needle aspiration of involved areas, but this procedure is associated with a significant incidence of complications. Open lung biopsy is probably preferable and avoids the contretemps of missing the

affected area of the lung. Like transtracheal aspiration, lung biopsy for diagnosis is required only infrequently.

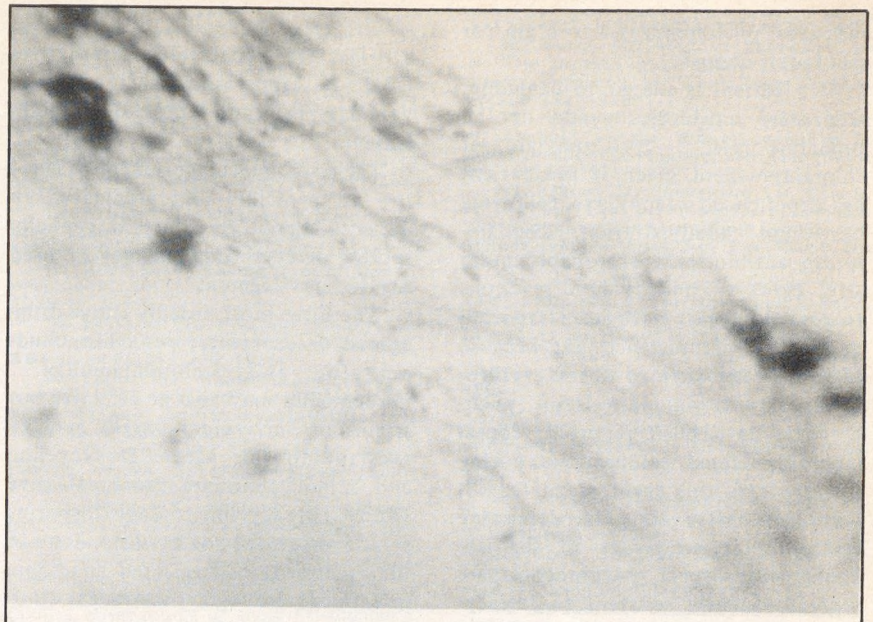

Figure 7. *Klebsiella pneumoniae* appears as fat encapsulated rods that usually stain red in a gram-stained smear.

Management of Infectious Pneumonias

A general overview of the various approaches to management of infectious pneumonias is shown in Table 2. The precise use of antibiotics is an essential foundation of effective treatment and will be considered in some detail.

Antibiotics

It is said that sputum specimens are invalid and that proper treatment is dependent on obtaining specimens by transtracheal puncture. This is nonsense. In point of fact, treatment almost always must be started before culture results are known and in the overwhelming majority of cases, appropriate regimens can be chosen by considering the data obtained by taking an adequate history, doing a careful physical examination, evaluating expectorated sputum for cells and organisms, and examining the chest x-ray. Only rarely is transtracheal puncture required.

When choosing antibiotics, it is also important to consider the time of year, epidemiologic circumstances, and the presence of underlying disease (such as chronic bronchitis) that might predispose to certain specific infections. The presence of suppurative extrapulmonary foci of involvement and allergic history are other important factors in choosing an antimicrobial agent. Penicillin G is still the best antibiotic for pneumococcal pneumonia. The pneumococcus has remained exquisitely sensitive to this antibiotic through the years. In an uncomplicated case of putative pneumococcal pneumonia in a previously healthy adult, penicillin dosage of 1.2 to 2.4 million units per day, given intramuscularly for seven to ten days should suffice. Oral administration of various penicillin preparations can be substituted after a few days of intramuscular injections. There is no evidence that higher doses effect recovery or improvement more rapidly and use of higher doses increases the risk of colonization and suprainfection with resistant organisms.[52] Ampicillin, given by mouth, or occasionally parenterally, is just as effective as penicillin; adequate dosage for pneu-

Table 1. Complications of Transtracheal Aspiration

Hemoptysis
Localized subcutaneous emphysema
Mediastinal emphysema
Subcutaneous abscess
Vasovagal reactions
Death

Table 2. Management of Patients with Infectious Pneumonia

Antibiotics
Adequate tracheobroncial toilet
Drainage of abscesses — if any — postural or surgical
Supportive treatment for the seriously ill:
Oxygen inhalation
Ventilatory support — endotracheal intubation and/or tracheostomy, if necessary
Fluid and electrolyte replacement
Monitor for superinfection
Monitor for antibiotic side effects
Maintenance of adequate nutrition
Control of any underlying cardiopulmonary or other systemic disease

mococcal pneumonia is 4 to 6 gm per day (adult dosage).

If a patient is allergic to penicillin, alternative antibiotics would be the cephalosporins,[53] erythromycin, or chloramphenicol. Even if the patient has experienced anaphylaxis following penicillin administration, cephalosporin antibiotics are probably quite safe. However, anaphylactic reactions to cephalosporins have been reported under such circumstances and because of this we are inclined to use erythromycin. Erythromycin-resistant pneumococci have been reported; consequently, failure to improve during therapy with this agent mandates obtaining in vitro tests to determine erythromycin sensitivity of the isolated pneumococci. Pneumococci are more frequently resistant to tetracycline, but over 90 percent of strains remain sensitive.[54] In the presence of extrapulmonary pneumococcal suppurative complications, higher doses of penicillin should be given, using 10 to 24 million units daily, if joints, the pericardium, or the meninges are involved.

In a patient suspected of having *Klebsiella* pneumonia, it has been common practice, especially in a seriously ill patient, to combine a cephalosporin and an aminoglycoside, either kanamycin, gentamicin, or tobramycin. Chloramphenicol, or tetracycline plus streptomycin, have also been found to be effective in Friedlander's pneumonia. It is our feeling that a cephalosporin should not be used alone in Friedlander's pneumonia, but others contend that cephalosporins alone are perfectly satisfactory, if the organism is sensitive to those agents (and most low serotype Klebsiellae are).

Hemophilus influenzae strains are generally susceptible to ampicillin, tetracycline and chloramphenicol. Increasingly, however, *H. influenzae* strains are being found to be resistant to ampicillin; in such cases chloramphenicol is the most dependable alternative available for general use.[55-57]

Any of the anti-staphylococcal, semi-synthetic penicillins (oxacillin, methicillin, nafcillin, cloxacillin, dicloxacillin) may be used for the treatment of staphylococcal pneumonia. Penicillin should be avoided unless the antimicrobial sensitivity patterns show that the staphylococcus is penicillin-sensitive. At least half of extra-hospital-acquired staphylococcal strains resist penicillin. In a patient allergic to penicillin, alternatives would be cephalosporins, lincomycin, vancomycin, and probably clindamycin.

The streptococci are generally sensitive to penicillin and ampicillin. In patients allergic to penicillin, cephalosporins or erythromycin may be used as alternative agents.

The three most broadly active drugs against anaerobes are penicillin, clindamycin, and chloramphenicol.[58] Carbenicillin may also be effective but strains of *Bacteroides fragilis* may be resistant to this agent. Doxycycline and minocycline are more effective than tetracycline. Cephalosporins should probably not be used alone in the treatment of suspected anaerobic infections, although some recent studies suggest that *B. fragilis* is not of major importance in lung infections and that consequently cephalosporins are adequate in putrid pneumonia since they are effective generally against other anaerobes.

For the treatment of gram-negative infections, kanamycin, gentamicin, tobramycin, colistin, or chloramphenicol may be used. For *Pseudomonas* infections, gentamicin, tobramycin, or carbenicillin may be used singly or in combination; in life-threatening *Pseudomonas* pulmonary infection, gentamicin or tobramycin should probably be combined with carbenicillin.[32] The combination is particularly recommended if the pneumonia supervenes in patients with underlying hematopoietic malignancy. Ampicillin may be used for most infections due to extra-hospital-acquired *E. coli* or *Proteus mirabilis*. In serious nosocomially acquired pneumonias due to *E. coli* or species of *Klebsiella, Enterobacter* or *Proteus*, gentamicin, tobramycin, or amikacin is recommended. Some feel that if the infection is life-threatening, another agent to which the organism is sensitive in vitro should be added. However, there is no proof the combination is more effective than the aminoglycoside alone (providing, of course, that the organism is sensitive to the aminoglycoside in vitro and adequate dosages are administered).

Mycoplasma pneumoniae organisms generally are susceptible to erythromycin or tetracycline. Tetracycline is also used for the treatment of ornithosis and Q-fever. Fungal infections are generally treated with amphotericin B, but this is ineffective in infections due to higher bacteria such as *Actinomyces israeli* or *Nocardia asteroides*. *Actinomyces* infections are best treated with penicillin or tetracycline. *Nocardia* infections usually respond to sulfonamides alone or in combination with other agents. There are now a variety of other regimens, the most promising of which is trimethoprim-sulfamethoxazole.

Tuberculous pneumonia can be treated with isoniazid combined with ethambutol and/or streptomycin. In severely ill patients, a combination of rifampin and isoniazid is probably the best regimen; with this regimen, patients, particularly those over age 35, must be observed closely for hepatic toxicity. Ethambutol, if given in improper dosage (over 15 mg/kg/day), may give rise to visual toxic effects, the earliest of which is loss of green color perception.

The treatment of choice for pneumocystis infection is pentamidine isethionate.[59] If given promptly, this agent is quite effective. Recent data suggest trimethoprim-sulfamethoxazole may be equally or even more effective.

Other Therapeutic Approaches

Antibiotics are so beneficial in most pneumonias and the physician depends on them so heavily that certain crucial supportive measures are often ignored. Several points merit emphasis:

1. Assiduous efforts must be made to clear tracheobronchial secretions using proper suction techniques and, where necessary, supplemental bronchoscopy.

2. If the patient continues to have respiratory distress or fails to clear an infiltrate, it is imperative to search for a mucous plug or foreign body. In such cases physical examination often shows diminished breath sounds over the involved area.

3. In a patient who smokes over one-half pack of cigarettes daily, any bacterial pneumonia must be evaluated from the point of an obstructing bronchial neoplasm. Diminished breath sounds in the involved area, a localized wheeze, or delayed resolution virtually mandate bronchoscopy and examination cytologically for abnormal cells. In the past, it has been said that

bronchoscopy should be performed in all patients above age 40 with putrid pneumonia. This is no longer so. If a person begins to smoke heavily at age 11 or 12, lung carcinoma can supervene in the late 20s or early 30s. It is thus mandatory to obtain a careful smoking history, including age of onset, and to consider the possibility of lung cancer in any person who has smoked heavily for more than 10 to 15 years.

4. In any patient suffering from pneumonia, it is essential to make sure that blood oxygen saturation is adequate. If severe hypoxia is allowed to persist, the patient may die even if the pneumonia is treated appropriately with antimicrobials.

5. In patients hospitalized with large lung abscesses, immediate consultation with thoracic surgeons should be obtained. If the response to antimicrobial agents is not prompt, or if the patient is overwhelmingly ill, surgical drainage or extirpation of the abscess may be life-saving.

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food models should be utilized as a basis for the collection of the food intake data to insure comparability between interviews.

The seven-day or three-day food records can provide a more representative measure of individual food intake than the 24-hour recall, particularly if administered frequently and consistently. However, since the participant himself completes the record, accuracy and comparability of data are not as good. This can be partially controlled by training the participant to keep the record and teaching him how to measure or estimate portion sizes and identify critical descriptive qualities of foods which alter or influence nutrient intake. Participants must also be highly motivated, since the production of accurate and complete records is a time-consuming and tedious task, particularly when done frequently.

Food pattern or preference questionnaires cannot provide specific qualitative and quantitative data on daily food intake. However, both do provide information as to the trends or frequencies within the usual food pattern. These data are useful not only for descriptive purposes, but also as an initial tool for assessment or diagnosis.

The limitations of each method have been partially overcome by utilizing more than one method per study, selecting reasonably representative samples of the population, and repeating the measurement several times in order to reduce both day-to-day variations and seasonal fluctuations of dietary intake. Also, repeating the studies in several different subsamples within the same region has been utilized to test the consistency of the results. The analysis of the relationship between the distribution of blood lipid levels and specific nutrient intake includes: calories, fat, carbohydrates and proteins, and specific types of fats. Many studies have also included the interrelationships between the nutrient and other variables that might influence the blood lipid levels, such as physical activity and "stress."

Investigators have attempted to control the interrelationships of nutrients in the diet by selecting comparisons among countries similar for most nutrients except for one or two specific items of interest, or studying countries with markedly different dietary patterns. For example, investigators have attempted to study the distribution of blood lipid levels, cholesterol, and triglycerides in countries where refined sugar intake is high but fat intake is relatively low. Another approach would be to adjust the levels of one nutrient in the statistical analysis. Often, however, the epidemiologist will need the help of the animal experimentalist to verify the conclusions of these field studies.

The results of the numerous descriptive and analytic epidemediologic studies have clearly demonstrated that the variations of blood lipid levels among populations in different countries were a function of the amount or percent of calories in the diet from saturated fat and cholesterol.

The next important step was to relate the levels of cholesterol among individuals within a geographic area or country to their specific nutrient intakes. For example, if participant A had a serum cholesterol level of 280 mg/100 ml and participant B had a level of 220 mg/100 ml, are the differences due to a higher dietary intake of fat for participant A as compared to participant B? The critical test is to determine the dietary differences between participants A and B as follows:

1. If there is a difference in dietary intake between A and B, how large is the difference in relation to the serum cholesterol levels?
2. What are the thresholds of the instruments being used to measure dietary intake variations from day to day?
3. Are the tolerances of the instruments greater than dietary differences between the two individuals?
4. If the instruments are just barely able to identify the dietary differences between A and B, will it require a very large sample of As and Bs in order to ascertain significant differences between them?
5. What is the variability of A's diet from day to day as compared to the differences in dietary intake between A and B?

If the variability of A's diet is greater than the differences in A's and B's diet on any specific day, it might not be possible to measure the differences between the two. The best approach would obviously be to mea-

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