Medical Grand Rounds
Parkland Memorial Hospital
November 21, 1985

NOSOCOMIAL PNEUMONIA

Galan B. Toews, M.D.

INTRODUCTION

Pneumonia, a microbial infection involving the terminal airways and alveoli of the lung, is an ancient respiratory affliction which constituted a leading cause of fatality in the pre-antibiotic era. In the first volume of the second edition of the Osler-McCrae Textbook, *Modern Medicine* (1), published in 1913, the third longest chapter, nearly 45,000 words in length, was devoted to the topic of lobar pneumonia. Among all the infections, it was surpassed in importance in the text only by typhoid fever and tuberculosis.

While pneumonia is an historically important illness, it is also a timely and rapidly evolving clinical subject. It is a disease that, during the recent decades of spectacular progress in the control of infectious diseases, many expected to be greatly ameliorated or eradicated altogether. In 1946, Alexander Fleming provided us with strong assurances that "...in the last ten years more advances have been made in the chemotherapy of bacterial infections than in the whole history of medicine. Penicillin is the most powerful therapeutic drug yet introduced...inhibiting the growth of staphylococcus even when diluted...and effective if the natural protective mechanism of the body is deficient" (2). This promise has not yet been realized. Many microbes can infect the lungs and they have proved to be so adaptable and hardy throughout the years of antibiotic onslaught that pneumonia still exists and is quite prevalent. From the introduction of the first antimicrobial agents, microorganisms have been outwitting man in his ability to provide effective chemotherapeutic agents.

There is no question that the specter of pneumonia is less awesome than before the antibiotic era and some common infectious causes are no longer worrisome because good antibiotics exist to combat them. However, from the numerous reports in recent years about new microorganisms causing pneumonia or unusual microbes infecting normal and immunosuppressed patients, one must conclude that pneumonia remains an important disease. A particularly problematic group of pneumonias are those that are acquired in a hospital environment or nosocomial pneumonias. There is abundant evidence that nosocomial pneumonias are a major cause of human suffering and death. Social, ethical, legal, financial and medical implications of these potentially preventable infections are considerable. Thus, this presentation will review recent developments in our understanding of nosocomial infections in general and nosocomial respiratory infections in particular.

DEFINITION

Nosocomial respiratory infections are those that develop in hospitalized patients in whom the infection was either not present or not incubating at the time of admission (3). Nosocomial infections are usually not manifest in the first 72 hours of hospitalization. For some lower respiratory tract infections, the recognition that incubating infections should not be classified as nosocomial is of importance; for example, the patient who develops influenzal pneumonia 24 hours after admission to the hospital or the patient who may have aspirated oral/pharyngeal material several days before admission and who then goes on to develop a necrotizing pneumonia with community acquired organisms after hospitalization should not be classified as having nosocomial pneumonia. Likewise, it is important to recognize that nosocomial infections may be incubating at the time of discharge from the hospital; hence,

they may be initially recognized at the time of outpatient follow-up. Although the delayed appearance of disease is more frequent with infections involving other sites than the lung, such delay may occur with nosocomial respiratory examples such as tuberculosis.

Establishing a diagnosis of nosocomial pneumonia may be particularly difficult. The disease is most common in critically ill patients who may not be able to report symptoms accurately and in whom the primary disease may mask or simulate the occurrence of bacterial pneumonia. In the intensive care unit setting, many patients have fever and leukocytosis from their primary disease process. Antecedent densities in the chest radiograph and purulent sputum also are common. Gram-negative bacillary pathogens are found in the sputum of a high fraction of patients with or without pneumonia. For this reason the diagnosis of pneumonia or lower respiratory tract infection is dependent upon clinical observations, including radiographic, rather than being based solely or predominantly on microbiologic findings.

Different clinicians and investigators have employed differing criteria for the diagnosis of lower respiratory tract infections. Wenzel and associates used the finding of infiltrate on chest radiography that was not present on admission and that is associated with new sputum production as a criterion for nosocomial pulmonary infection (4). Johansen and colleagues have utilized more stringent criteria and have classified infections as "definite" or "probable" according to four determinants: 1) The radiographic appearance of a new or progressive pulmonary infiltrate, 2) Fever, 3) Leukocytosis, and 4) Purulent tracheobronchial secretions. A diagnosis of "definite" infection required the occurrence of all four determinants. A diagnosis of "probable" infection is based upon three critera: 1) Fever, 2) Leukocytosis, and 3) Either a new or progressive pulmonary infiltrate (5). The criteria for diagnosis of nosocomial respiratory infection that are currently being used by the National Nosocomial Infection Study (NNIS) and in the Study on the Efficacy of Nosocomial Infection Control (SENIC) Project appear to offer a reasonable compromise in sensitivity and specificities (6, 7). In adults there must be an onset of purulent sputum production more than 48 hours after admission in a patient with no preceding lung infection or increase in sputum production with recurrence of fever in a patient admitted the the hospital with pulmonary disease. One of the following findings must also be present: 1) Infiltrate on chest radiograph or physical findings consistent with pneumonia in the absence of a chest radiograph; or 2) Pleuritic chest pain, cough and fever. The diagnosis of pneumonia by the attending physician is accepted when these criteria are incomplete. Suprainfection may be diagnosed in a patient with nosocomial pneumonia when a new pathogen is cultured from sputum in association with appropriate clinical and chest radiographic deterioration. Despite the reasonableness of these critera for diagnosis of nosocomial respiratory infection, there is likely a 30 percent false-positive and false-negative diagnosis of pneumonia when these guidelines are used (8).

IMPACT OF NOSOCOMIAL PNEUMONIA

Incidence and Prevalence

Much of our current information concerning nosocomial infections comes from the National Nosocomial Infections Study (NNIS) that was initiated by the Centers for Disease Control in 1969 and continues to the present (9, 10). In 1979, 82 hospitals in 31 states regularly reported nosocomial infections to the NNIS; 44,785 infections occurred in 1,362,342 hospitalized patients. The mean rate of nosocomial infections in 1971 was 3.8 percent of acute care patients discharged

from reporting hospitals. This rate has fallen to 3.6 percent in 1975 and 3.3 percent in 1979. The reason for this decrease in overall rate of infection is not clear. Infection rates for community teaching and municipal hospitals have declined; rates for community and university hospitals have not.

These statistics were reported from only 82 hospitals among the nation's several thousands of health care institutions; caution has been urged in generalizing from these data to the individual hospitals. In a study that parallels the NNIS, the Study of the Efficacy of Nosocomial Infection Control (SENIC) Project, estimates of the frequency of nosocomial infections were based on a stratified random sample of 169,526 adult , general medical and surgical patients selected from 338 hospitals representative of the main stream of hospitals in the United States from 1975 to 1976. In the mid 1970s one or more infections developed in 5.23 percent of patients hospitalized in the United States and 6.62 infections occurred among every 100 admissions (11). Exact comparisons between these studies are hampered by differences in methodology and reporting techniques. The most frequent types of nosocomial infection are urinary (42%), surgical wound infections (24%), pneumonia (11%), blood stream infections (5%) and others (18%) (12).

Table 1

Relative Frequency of Nosocomial Infections
By Site of Infection

Site	%
Urinary tract	42
Surgical wound	24
Pneumonia	11
Blood stream	5
Others	18

Haley, Am. J. Epidemiol. 121:159, 1985

Adverse Consequences of Nosocomial Infections

The consequences of nosocomial infections are considerable in terms of human suffering, loss of life and cost. Studies which estimate the adverse consequences of nosocomial infections usually rely on estimates of prolongation of hospital stay, extra hospital costs or charges, and death as indicators of the consequences of nosocomial infections. Extra days of hospitalization due to nosocomial infection analyzed by site of infection are shown in Table 2. Nosocomial pneumonia is second only to surgical wound infection in causing extra hospital days.

Table 2

Extra Hospital Days Resulting From Nosocomial Infection

Site	%
Surgical wound	57
Pneumonia	24
Urinary tract	11
Blood stream	4
Other	4

Haley, Am. J. Med. 70:51, 1981

While estimates of extra hospital charges do not necessarily accurately represent actual hospital costs, the latter are difficult to obtain and study. Thus, hospital charges to patients are usually used as a substitute for actual costs. If one attempts to evaluate the economic burden of infection by site of infection, a similar ranking to that obtained for extra days is noted (Table 3).

Table 3

All Extra Charges Attributable to Nosocomial Infections

Site	%
Surgical wounds	42
Pneumonia	39
Urinary tract	13
Blood stream	3
Other	3

Haley, Am. J. Med. 70:51, 1981

Pneumonias are somewhat more expensive to care for on average than surgical infections even though surgical infections cause more total days. From this analysis, it is clear that a great majority of the extra costs attributable to nosocomial infection are related to surgical wound infections and pneumonias.

Nationwide estimates of the number of deaths attributable to nosocomial infections have varied widely. By combining data from the SENIC project and from a concurrent assement of mortality performed in NNIS (13) it is estimated that nosocomial pneumonia directly causes death in 3.1 percent of patients and contributes but is not the only cause in 10.1 percent of patients. In a recent

study, this issue was approached from a different perspective (14). The hospital courses of 200 consecutive patients who died were reviewed for evidence of nosocomial infection. Infection was present in 32 percent of patients who died. Pneumonia accounted for 40 percent of all nosocomial infections. Furthermore, pneumonia accounted for 60 percent of patients who died as a direct or indirect result of nosocomial infection.

An estimate of the magnitude of the problem of nosocomial pneumonias is provided in summary in Table 4. The SENIC project estimated that a nosocomial respiratory infection develops in approximately 1 percent of patients admitted to the hospital. Using this estimate of incidence and an estimate of approximately 38 million hospital discharges from non-federal, short stay hospitals in 1980 (15), a nosocomial respiratory infection would be expected to develop in 380 thousand patients per year. Another method of estimating the total number of nosocomial pneumonias per year yields similar results. The total number of nosocomial infections in the United States per year range between 1.5 and 2 million (16). Since nosocomial respiratory infections cause about 15 percent of all nosocomial pneumonias, a similar estimate of 225 to 300 thousand nosocomial infections occur per year. If the direct fatality rate of these patients is approximately 3 percent per year, then 7500 patients die each year as a direct result of nosocomial pneumonia. Additionally, it is estimated that nosocomial pneumonias contribute to the cause of death in an additional 10 percent of cases, accounting for an additional 25,000 deaths. Finally, nosocomial pneumonias also generate considerable additional health care costs. Nosocomial pneumonia adds approximately 6 days to the hospital stay of infected patients and results in approximately 5 thousand 1985 dollars of extra charges per patient infected. These costs result in total extra charges of approximately 1.1 billion 1985 dollars.

Table 4

Estimate of the Magnitude of the Problem of Nosocomial Pneumonia

Incidence (%)	1
Total patients/yr	250-400,000
Direct fatality rate (%)	3
Infections directly causing death	7500
Contributing fatality rate	10
Infection contributing to death	25,000
Extra days	6
Extra charges/patient (1985 $)	5000
Total extra charges (billions of 1985 $)	1.1

CDC, NNIS Report, March 1982
Haley, Am. J. Med. 70:947, 1981
Haley, Am. J. Med. 70:51, 1981

CAUSES OF NOSOCOMIAL LOWER RESPIRATORY TRACT INFECTIONS

Currently the best source of information for gaining insight into the nationwide patterns of microorganisms involved in nosocomial infection is the NNIS. In the report of data from 1980-82 the epidemiology of the various nosocomial pathogens was particularly well analyzed (17). Cultures were obtained in 90 percent of reported nosocomial infections and in 85 percent at least one causative pathogen was isolated. A single pathogen was found in 65 percent and more than one pathogen was found in 20 percent. Among these infections of known cause, 91 percent involved aerobic bacteria, 2 percent anaerobic bacteria, 6 percent fungi and the remaining 1 percent a miscellaneous group of viruses, protozoa and parasites.

Nosocomial lower respiratory tract infections may be caused by virtually any microorganism including aerobic gram-positive cocci, aerobic gram-negative bacilli, anerobes and viral, mycoplasmal, chlamydial, fungal, mycobacterial and parasitic organisms. The NNIS provides reasonable estimates regarding the frequency of aerobic bacteria as causative agents of nosocomial respiratory infections. These data and statistics from other sources clearly show the importance of aerobic gram-negative bacilli in nosocomial respiratory infection with 60 to 80 percent of nosocomial respiratory infections being caused by these organisms (17). While the spectrum of organisms causing lower respiratory tract infection has changed from the 1950s when gram-negative bacilli accounted for only 1/3 of nosocomial respiratory infections (18),it can be seen in Table 5 that little change in the microbiology of nosocomial respiratory infections has occurred in the last decade.

Table 5

Etiology of Nosocomial Pneumonia
And Lower Respiratory Infections

Causative Agents	1970-1973	1980-1982
	%	%
Klebsiella sp	15.4	13.4
P. aeruginosa	13.5	13.1
S. aureus	12.6	13.0
Enterobacter sp	9.1	9.5
E. coli	11.0	8.0
Proteus sp		5.8
Serratia sp	2.0	5.1
Candida		4.0
Enterococci		1.7
Streptococcus, group B		1.0
Staphylococci, Coagulase Negative		0.8
Bacteroides sp		0.3
S. pneumoniae	8.0	
All Others	28.4	24.3

Hughes, Morb. Mort. Weekly Rep. 32:155, 1983

In recent years, with the marked increase in population of patients who are immunocompromised as a result of transplantation or chemotherapy, numerous reports have documented the prevalence of respiratory tract infectious disease in these patients. These patients often have unusual causative pathogens; fungi, including *Aspergillus* (19, 20), *Mucor* (21), *Candida* (22), *Cryptococcus* (23, 24); protozoa, including *Pneumocystis carinii* (25, 26) and *Toxoplasma gondii* (27); viruses, including cytomegolovirus (28-30), herpes simplex (31), herpes zoster (31), respiratory syncytial virus (32), parainfluenza (33), influenza A (34, 35) and influenza B (36) and the bacteria, including *Nocardia* species (37, 38), tuberculosis (39), atypical mycobacteria (40), *Legionella pneumophila* (41-45), *Legionella micdadea* (46, 47) and *Chlamydia trachomatis* (48). Further, in a recent prospective study, *Haemophilus influenzae* an organism usually associated with community acquired infections, was implicated in 29 percent of nosocomial respiratory infections at one institution (49). It seems likely that additional microorganisms will be identified as causative agents in nosocomial pneumonia in the future. Various parasites, for example that are uncommon in the United States will likely be implicated in nosocomial infections in other parts of the world.

PATHOGENESIS

Since aerobic gram-negative bacteria cause a majority of nosocomial pneumonias, this review will concentrate on the pathogenesis of these infections. Bacteria that cause pulmonary infection are inoculated into the respiratory tract by four mechanisms: 1) inhalation of airborne organisms, 2) aspiration of oropharyngeal contents, 3) direct extension from contiguous sites, and 4) hematogenous spread from sites of infection elsewhere in the body. While microorganisms from the environment or skin may be deposited in the lung or pleural space in trauma victims with penetrating chest wounds, and distant sites of infection can disseminate into the lung, as a practical matter, respiratory tract infection caused by the latter two routes of inoculation is relatively uncommon and the primary site of infection is usually of greatest importance. This discussion will thus focus on infections produced by the former two routes of inoculation, that is inhalation of airborne organisms and aspiration of oropharyngeal contents.

Airborne Nosocomial Infections

The concept that bacterial pneumonia may be acquired by inhalation of airborne organisms has been popular for over a hundred years. However, early attempts to produce pneumonia by exposing experimental animals to aerosolized bacteria were generally unsuccessful and the general concept of the transmission of infectious agents through the air came under serious question. A clinical circumstance which occurred at Parkland Memorial Hospital clearly documents that bacterial pneumonia can be initiated by inhalation of airborne organisms. In the mid 1960s it became apparent that inhalation therapy equipment used in hospitals was frequently contaminated with bacteria, commonly *Pseudomonas aeruginosa* (50). Therefore, ill patients received massive daily inoculations of airborne organisms in the respiratory tract. Over 70 percent of nebulizer devices at patient's bedsides were contaminated and 12 percent of subjects coming to autopsy had gram-negative necrotizing pneumonia (51). The incidence

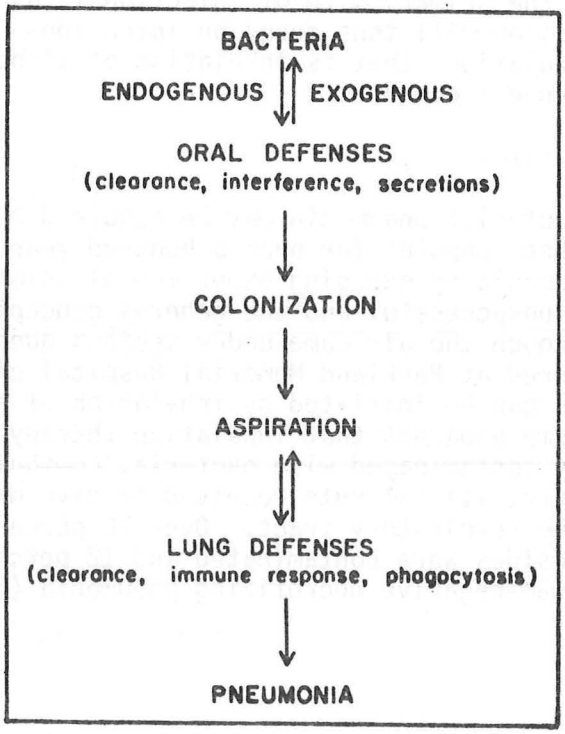
of necrotizing pneumonia at autopsy decreased with the decreasing frequency of contaminated respiratory therapy equipment in the years that followed (52) and continued surveillance programs show that contamination of respiratory therapy is now uncommon largely because of the virtually universal use of disposable equipment and the widespread understanding of this potential problem. In the absence of this nosocomial hazard, little data exists to suggest that hospitalized patients are at risk from airborne gram-negative bacteria. The organisms found in hospital air are generally nonpathogenic and compared with the numbers required to produce infection in experimental animals, these organisms are present in very low numbers (53). Attempts to reduce various infections by techniques designed to reduce bacterial contamination of the air by ultraviolet irradiation, controlled air flow, or high volume ventilation have generally had little impact on the occurrence of pneumonia. Definite exceptions to the general observation are known to occur and include the nosocomial outbreaks of *Legionella* pneumonias, nosocomial aspergillus pneumonia, nosocomial acquisition of *M. tuberculosis*, and outbreaks of hospital associated viral infections.

Aspirational Nosocomial Pneumonias

Most bacterial pneumonias in hospitalized patients are due to aspiration of oropharyngeal contents. The infecting organisms are resident, either transiently or persistently in the upper respiratory tract and organisms are presented to the lung in a liquid bolus rather than as a finely dispersed aerosol. The pathogenetic steps involved in this infection are therefore different from those just described and include: 1) colonization of the upper respiratory tract, 2) aspiration into the tracheobronchial tree, and 3) interaction with antibacterial pulmonary defense mechanisms (Figure 1).

Figure 1

Pathogenesis of Nosocomial Infections of the Lower Respiratory Tract



LaForce, Am. J. Med. 70:664, 1981

Colonization: In normal persons, colonization of the mucosal surfaces of the upper respiratory tract is achieved by a variety of anaerobic and aerobic organisms. The bacterial flora of the upper respiratory tract in a given person remains constant for a long time, but it varies among normal persons. Factors that have been proposed to account for the selective aspects of this colonization include physical attributes of the local milieu, such as redox potential, salivary flow, interbacterial interference in which one species of bacteria inhibits the growth of another and the chemical nature of secretions including IgA and lysozyme (54). However, the predominant mechanism determining the selection of those organisms that successfully colonize the upper respiratory tract is likely bacterial adherence to epithelial cells. Considerable new information exists in this regard and will be reviewed in some detail.

Enteric gram negative bacteria are relatively uncommon inhabitants of the upper respiratory tract being present in 2 percent of normal persons (55). However in patients who become seriously ill, colonization of the upper respiratory tract by gram-negative bacilli occurs swiftly. The prevalence of such colonization correlates with the severity of the patient's illness and is present in approximately 50 percent of patients requiring care in intensive care units (56)(Table 6). Because nosocomial pneumonias occur almost exclusively in individuals who are colonized and because the organism causing the pneumonia is identical to the organism with which the patient is colonized, it seems reasonable to believe that colonization of the upper respiratory tract is an important pathogenetic feature of these infections and that alteration in mucosal adherence of gram-negative bacilli might be an important determinant of this process (Table 7).

Table 6

Results of Single-Culture Surveys

Study Group	No. of Subjects	Cultures Containing Gram-negative Bacilli
		%
Normal Subjects:		
Nonhospital Associated	82	2
Hospital Associated	47	2
Patients:		
Psychiatry Service	20	0
Moderately Ill	81	16
Moribund	23	57

Johanson, N. Engl. J. Med. 281:1137, 1969

Table 7

Risk of Hospital Acquired Pneumonia
ICU Patients

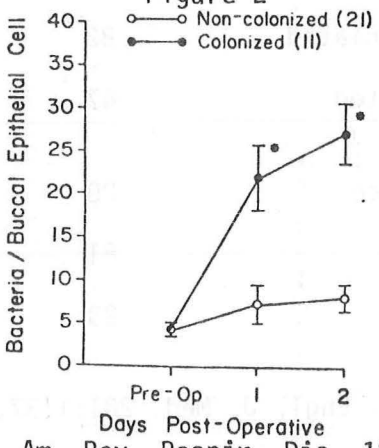
Number of Patients	GNB Colonization Number	GNB Colonization Pneumonia	No GNB Colonization Number	No GNB Colonization Pneumonia
582	207	41 (19.8%)	375	5 (1.3%)

Johnson, Ann. Intern. Med. 77:701, 1972
Northey, Surg. Gynec. Obstec. 139:321, 1974
Feeley, N. Engl. J. Med. 293:471, 1975

Bacterial adherence to mammalian epithelial cells is currently a popular area of investigation and many observations have been made of this phenomenon. However directly applicable the results appear in the understanding of human biology and disease, the *in vitro* conditions under which cell to cell interactions are observed and quantitated may differ radically from those *in vivo* and the situation may not be as straightforward as it appears. Despite this qualifier, this topic will be reviewed in some detail.

To investigate the temporal relationship between the onset of illness, buccal cell adherence properties and the occurrence of colonization, Johansen and colleagues studied 32 noncolonized patients who were scheduled for elective surgery (57). Preoperatively, buccal cells from these patients attached few *Pseudomonas aeruginosa* per cell *in vitro* and none of the patients was colonized with gram-negative bacilli. By the second post-operative day, 11 (33%) of the patients had become colonized. As shown in Figure 2, adherence was significantly greater among patients in the colonized group than in the noncolonized group. Colonization was never noted to occur in patients whose buccal attachment did not increase post operatively. The increased adherence of *P. aeruginosa* post-operatively was associated with similar increases in adherence of *K. pneumoniae*, *E. coli* and *P. mirabilis*. Differences in *in vitro* adherence of various bacilli could not be related to the organisms producing colonization *in vivo*.

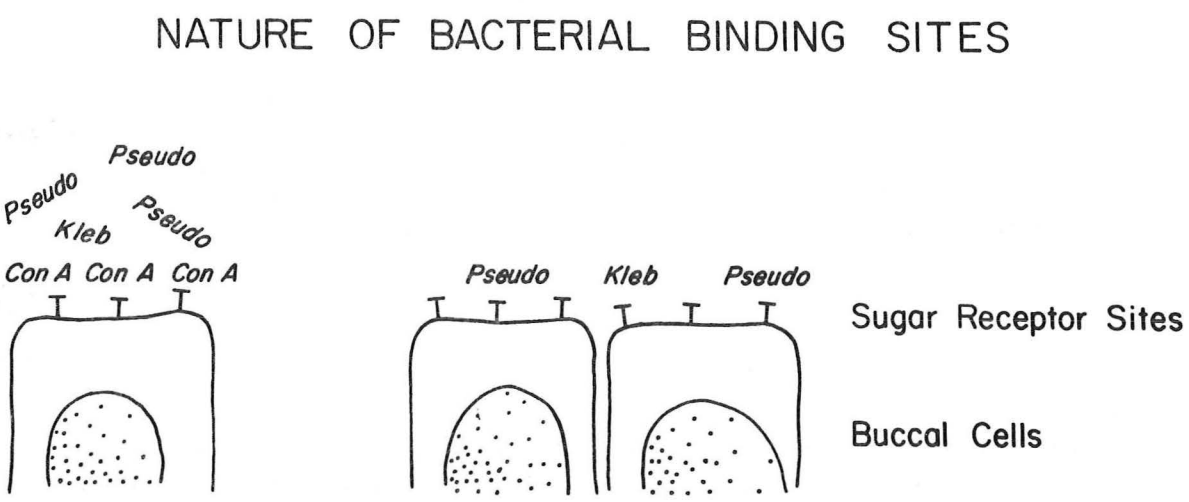
Figure 2



Johansen, Am. Rev. Respir. Dis. 121:55, 1980

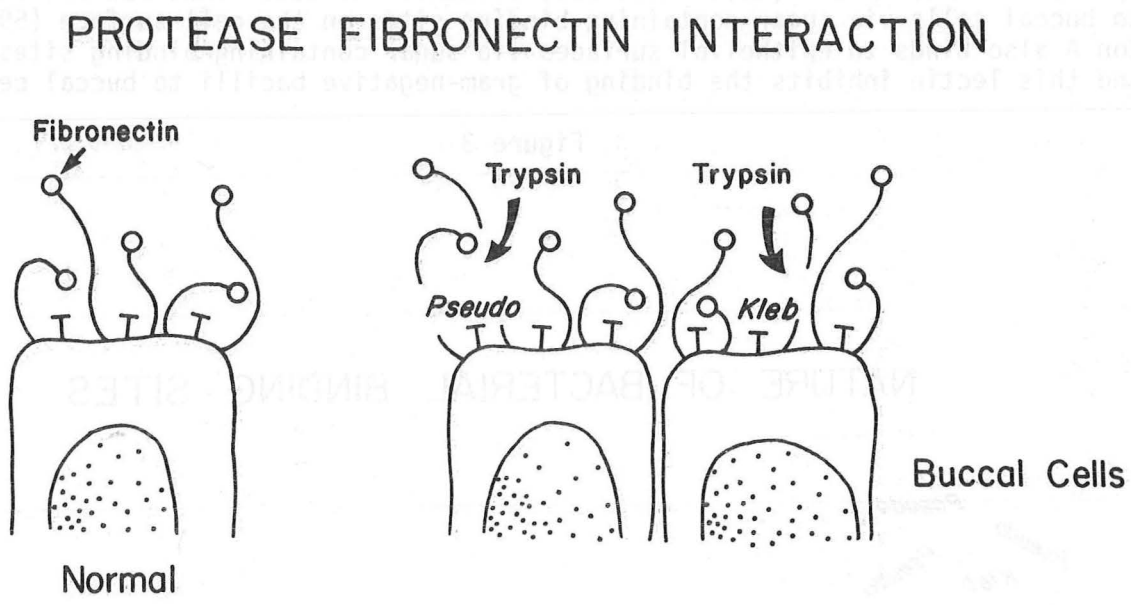
The mechanism of bacterial attachment to epithelial cells appears to involve the binding of specific molecules on the bacterial surface to binding sites on the cell (Figure 3). In the case of gram-negative bacilli, the bacterial binding site appears to be located on the pili since non-piliated strains of species fail to adhere (58). Available evidence indicates that bacilli adhere to buccal cells via sugar containing binding sites on the cell surface (59). Con A also binds to epithelial surfaces via sugar containing binding sites (60) and this lectin inhibits the binding of gram-negative bacilli to buccal cells (59).

Figure 3



Normal mammalian cells possess several defense mechanisms that function on mucosal surfaces to prevent bacterial colonization including the presence of secretory glycoproteins that inhibit bacterial adherence by competing with epithelial cell surfaces for bacterial binding sites (61) (Figure 4). Fibronectin, a large molecular weight protein is known to be present on the surface of normal oropharyngeal epithelial cells (62). Bacillary adherence to normal buccal epithelial cells could be increased *in vitro* by brief exposure of these cells to trypsin. Since fibronectin was known to be highly sensitive to trypsin, it was possible that proteases present in oropharyngeal secretions cleaved protective layers of fibronectin and exposed mucosal cell binding sites for gram-negative organisms.

Figure 4



This possibility was evaluated in patients undergoing coronary artery bypass surgery (63). As shown in Table 8, surgery was followed by a marked increase in buccal epithelial cell adherence of *P. aeruginosa*, a decrease in cell surface fibronectin, and an increase in proteolytic activity in oropharyngeal secretions. These abnormalities persisted several days but were returning toward baseline by day 4. Thirty-eight percent of patients studied became colonized with gram-negative bacilli. These data demonstrate that the alteration of upper respiratory tract epithelial cell surfaces occurs before the acquisition of colonizing gram-negative bacilli. The important changes appear to include loss of cell surface fibronectin; an alteration associated with an increase in proteolytic activity in secretions (Figure 5). The source of these proteases is not known. Loss of cell surface fibronectin could account for the decreased adherence of gram-positive organisms if that protein is involved in the binding of gram-positive organisms.

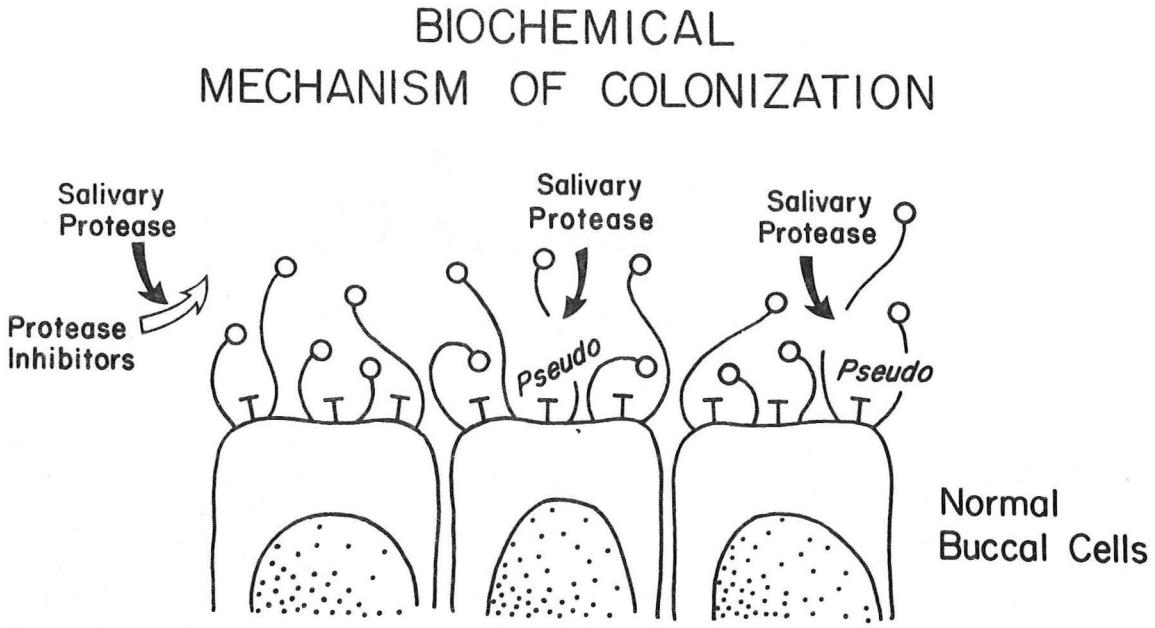
Table 8

Changes in *In Vitro* Adherence of *Pseudomonas aeruginosa* to Buccal Cells, Cell Surface Fibronectin, and Salivary Protease Activity

Days	*P. aeruginosa* Adherence *In Vitro*	Cell Surface Fibronectin	Salivary Protease Activity
	% Of Control		
0	132	96	114
1	650	19	298
2	725	18	283
3	283	55	151

Woods, J. Clin. Invest. 68:1435, 1981

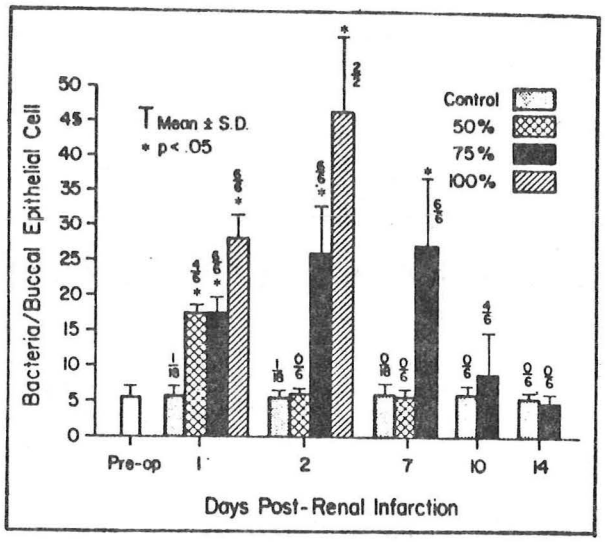
Figure 5



Similar results have been obtained from studies with experimental animals (64). In rats, a semi-quantitative surgical insult can be produced by graded infarctions of the renal parenchyma. This surgical procedure is associated with an increase in buccal cell adherence for gram-negative bacilli. In animals subjected to this procedure and inoculated postoperatively with *P. aeruginosa*, a progressive increase in buccal cell adherence correlated with the amount of renal tissue infarcted (Figure 6). Buccal cell adherence increased markedly following the surgical stress and all animals inoculated orally with *P. aeruginosa* became colonized, whereas none of the sham operated animals did. Both buccal adherence and susceptibility to colonization returned to normal in animals that underwent less than total renal infarction, although this improvement was prolonged in animals with extensive renal damage. These data suggest that the increased adherence of gram-negative bacilli to buccal epithelial cells in an *in vitro* assay correlates with susceptibility to acquisition of these organisms *in vivo*, a finding consistent with the previous study.

Figure 6

Serial Adherence Assays and Colonization Rates in Graded Renal Infarction



Johanson, Am. J. Med. 76:69, 1984

Thus, a large body of clinical and experimental observations exist which indicate that seriously ill patients rapidly acquire gram-negative bacilli in upper respiratory tract secretions and that persistent colonization of this region is associated with alterations in the mucosal adherence properties for these organisms. Presumably once established in the upper respiratory tract, these organisms may multiply and achieve high concentrations in respiratory tract secretions although serial quantitative studies of the latter phenomenon have not been reported.

The clinical conditions that promote colonization of the respiratory tract with gram-negative bacilli have also been studied (56) (Table 9). The

more gravely ill the patient, the more likely colonization is to occur. Indicators of the severity of illness associated with colonization in this study were coma, hypotension, sputum production, tracheal intubation, antimicrobial drugs, acidosis, azotemia and leukocytosis or leukopenia. The increased frequency of colonization among patients with respiratory disease, sputum production or endotracheal intubation suggests that conditions that impair lung clearance may also promote colonization. Although antimicrobial therapy almost surely plays some role in some patients, data from this study indicated that in most instances, colonization occurred independently of such therapy. The specific organisms which colonize a patient may come from the patient's gastrointestinal flora or may be transmitted to that patient from other colonized patients. The mode of spread is usually the hands of medical personnel.

Table 9

Variables Associated With Gram-Negative Bacillary Colonization of the Respiratory Tract in MICU Patients

Primary Diagnosis	Variables Significantly Correlated with Colonization
Overall	Coma, Hypotension, Sputum, Tracheal Intubation, Antimicrobial Drugs, Acidosis, Azotemia, Leukocytosis or Leukopenia
Cardiovascular	Hypotension, Expectoration of Sputum, Acidosis, Leukocytosis or Leukopenia
Respiratory and Drug Overdose	Coma, Sputum, Tracheal Intubation, Antimicrobial Drugs
Others	Leukocytosis or Leukopenia

$p < 0.05$

Aspiration: The aspiration of oropharyngeal secretions is thought to be the most important route of entry of bacteria into the lower respiratory tract. Bacterial inoculation of the lungs by aspiration of small quantities of oropharyngeal secretions was initially proposed in 1937 (65). Using more sensitive techniques than those employed by previous investigators, Huxley et al. (66) demonstrated that a substantial majority of patients with impaired consciousness have aspiration of oropharyngeal secretions during sleep as do about half of normal persons (Table 10). The technique employed by these investigators required the demonstration of radioactivity in the lung periphery and if aspiration of this magnitude could be demonstrated, then minute quantities of oropharyngeal secretions will most likely be aspirated during sleep in all

persons. It was the impression of these investigators that normal subjects who slept poorly or awakened during the injections had negative scans and that all subjects that slept soundly throughout the night were found to aspirate. It is important to have a clear understanding of the amount of these secretions that must be aspirated to produce significant contamination of the tracheobronchial tree. If gram-negative bacilli are present in upper respiratory secretions in concentrations of 10^7 to 10^8 organisms per mililiter, aspiration of only 0.001 to 0.0001 ml would produce a fluid bolus in the tracheobronchial tree containing 10^4 organisms per mililiter. As shall be discussed later, inoculation of the lower airways with this number of organisms in a liquid bolus is highly likely to produce infection in experimental animals. The presence of cuffed endotracheal tubes does not prevent the aspiration of small quantities of oropharyngeal secretions, apparently because they are milked around the cuff during respiratory cycles.

Table 10

Summary of Aspiration Study

	Scan Results		
	Positive	Indeterminate	Negative
Stuporous Pts. (n = 10)	70%	20%	10%
Normal Subjects (n = 20)	45%	25%	30%

Huxley, Am. J. Med. 64:564, 1978

Pulmonary defense mechanisms: Whether or not pneumonia develops in a given patient ultimately depends on the interaction between invading bacteria and host defenses. Quantitative aspects of respiratory antibacterial defenses were defined in a series of experiments by Green and Kass (67, 68) and Laurenzi (69) in the 1960s. These investigators initially used nonpathogenic staphylococci, well defined exposure conditions, and quantitative bacteriologic techniques to demonstrate that viable bacteria were rapidly cleared after airborne inoculation of the lung. Using radiolabeled bacteria they found that physical transport of the bacterium out of the lung contributed only a small fraction to the overall reduction in viable bacteria. Over a 4 hour period of time, a 10 fold decrease in bacterial counts was noted and most of this reduction was due to *in situ* bacterial killing. Parallel, morphologic and bacteriologic studies indicated that the resident population of alveolar macrophages was the principal phagocytic cell involved in the process for some species of bacteria. Phagocytosis of staphylococci on the alveolar surface apparently did not require humoral factors such as opsonic antibody or complement.

Table 11

Clearance of Pseudomonas aeruginosa in Normal and Granulocytopenic Mice

Group	% Bacteria Remaining
Normal	73 ± 10.6
Granulocytopenic	513 ± 51.3

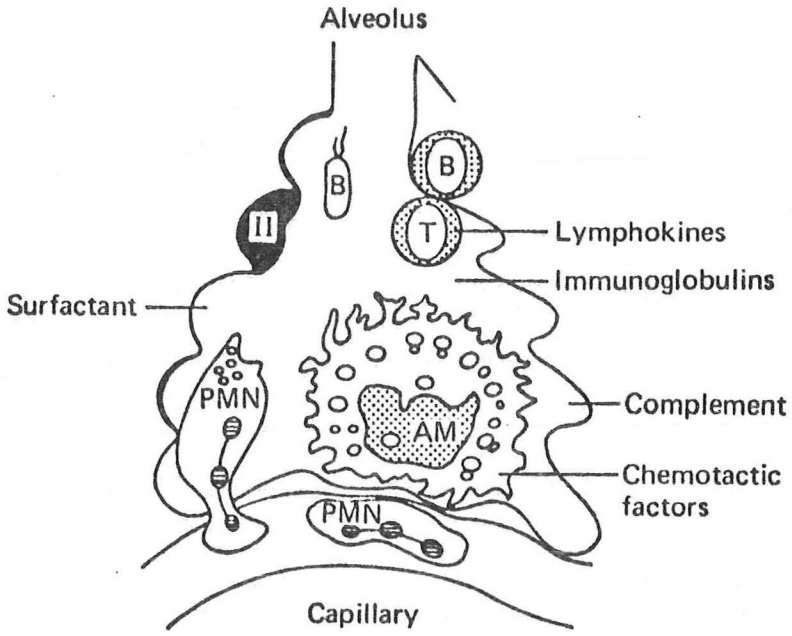
Rehm, J. Clin. Invest. 66:194, 1980

Defense of the lung against an airborne challenge of highly virulent bacteria is quite different. Although the normal lung is able to swiftly inactivate large numbers of pathogenic organisms, exposure to such agents evokes a brisk influx of polymorphonuclear leukocytes into the lung (70). The rate of bacterial clearance of *Streptococcus pneumoniae* and several gram-negative bacilli is enhanced by previous immunization of the animal and is impaired in the presence of complement deficiency (71). Using selective immunologic techniques to depress polymorphonuclear leukocytes, Rehm et al. (72) showed that polymorphonuclear leukocytes were far more critical to the pulmonary clearance of inhaled *Pseudomonas aeruginosa* than macrophages (Table 11).

These observations can be synthesized into a general concept regarding antibacterial defense of the lung against bacteria (Figure 7). For organisms with low virulence, resident antibacterial mechanisms, principally the alveolar macrophage, are sufficient. Histologic inflammation does not result from such exposures and the capacity of the lung to inactivate such challenges is truly enormous. For more virulent organisms, a far more complex mechanism exists which is only now becoming fully appreciated. The traditional concept of lower respiratory defenses as a combination of cough and mucociliary clearance plus alveolar macrophage mediated phagocytosis is inadequate to explain the operation of this system. With more virulent organisms circulating neutrophils and humoral factors become critical aspects of respiratory defense.

Figure 7

DEFENSE MECHANISMS OF THE LOWER RESPIRATORY TRACT



Despite the elegance of the preceding studies, their relevance to the development of pneumonia in patients at risk is uncertain. As mentioned previously, most bacterial pneumonias in compromised patients are believed to be due to aspiration of oropharyngeal contents. The organisms are presented to the lung in a liquid bolus rather than as a finely dispersed aerosol. When the lower airways of experimental animals are inoculated with a liquid bolus of bacteria, infection is highly likely (Table 12). Bolus inoculation of 10^4 *Streptococcus pneumoniae* or *Klebsiella pneumoniae* resulted in the universal development of pneumonia in experimental animals, whereas aerosol exposure to doses as high as 10^7 *Klebsiella pneumoniae* were effectively cleared (73, 74).

Table 12

Relationship of Method of Administration
To Bacterial Virulence in the Lung

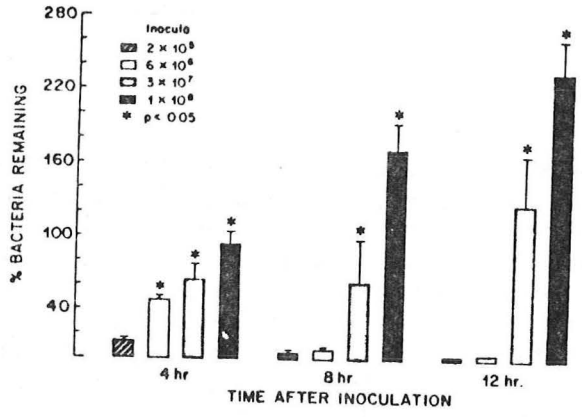
Method of Delivery	Inoculum	Result
S. pneumoniae		
Aerosol	10^5	Clearance
Bolus	10^4	Pneumonia
K. pneumoniae		
Aerosol	10^7	Clearance
Bolus	10^4	Pneumonia

Ansfield, Infect. Immun. 17:195, 1977
Johanson, J. Clin. Invest. 53:1320, 1974
Berendt, Infect. Immun. 20:532, 1978

More recent studies of host defense mechanisms in the lung have utilized such a bolus model. If experiments are repeated utilizing *S. aureus* in such a model, findings quite different from those of Laurenzi and Kass are obtained (75). The inoculum of bacteria delivered is critically important in such experiments as shown in Figure 8. While low inoculums are

Figure 8

CLEARANCE OF *S. aureus*

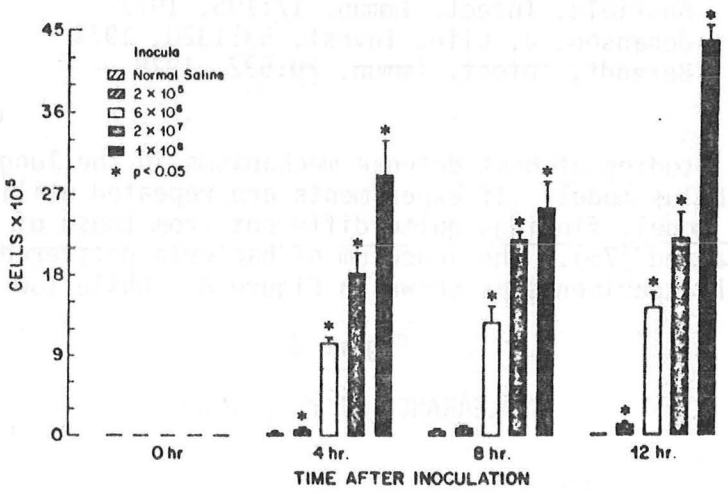


Onofrio, Am. Rev. Respir. Dis. 127:335, 1983

effectively cleared, increases in the inoculum of bacteria provided eventually lead to the development of pneumonia, even with this relatively nonpathogenic organism. Further, as shown in Figure 9, as the inoculum sizes increased, granulocytes are recruited to the lungs of these animals even in response to a relatively nonpathogenic organism. These findings suggest that there are sufficient numbers of alveolar macrophages on alveolar surfaces to successfully phagocytize and kill an inoculum of *S. aureus* if the initial bacteria to phagocyte ratio does not exceed some critical number. As the bacterial inoculum and hence this ratio increases, however, there are not enough alveolar macrophages to eradicate the organisms and PMN are recruited to the airspace. For even higher inocula, bacterial killing by the combination of phagocytes is delayed compared with that in smaller inocula but is ultimately successful in eliminating the organism. If the deposited bacterial inoculum is even larger, the resident alveolar macrophages and recruited PMN are insufficient to prevent bacterial multiplication and pneumonia ensues.

Figure 9

Granulocyte Recruitment in
Response to *S. aureus*



Onofrio, Am. Rev. Respir. Dis. 127:335, 1983

Thus, if the burden of microorganisms is large or virulent, an inflammatory response is required for effective clearance. The ability to develop an inflammatory response in lung tissues is an important and fundamental part of host defense that allows the lung to deal quickly and decisively with a variety of inhaled, aspirated or blood borne infectious agents. The mechanism(s) by which this inflammatory response is generated are being dissected. As shown in Table 13, normal resting lungs contain few polymorphonuclear leukocytes. It is thus likely that the presence of bacteria in alveolar spaces must trigger some signal that recruits these cells. Although accurate quantitative analysis of complement components in the lower respiratory secretions is both logistically and technically difficult, the C5 molecule has been shown to be importantly

Table 13

Recruitment of Neutrophils to the
Lung Following Bacterial Challenge

Bacterium	C5+	C5-
	Cells X 10^5	
S. pneumoniae (1 X 10^6)		
0 h	0.01	0.01
4 h	4.10	0.36
P. aeruginosa (2.5 X 10^6)		
0 h	0.04	0.04
6 h	65.0	21.0
24 h	64.0	45.0
48 h	24.0	92.0

Toews, Am. Rev. Respir. Dis. 129:82, 1984
Larsen, Am. Rev. Respir. Dis. 126:306, 1982

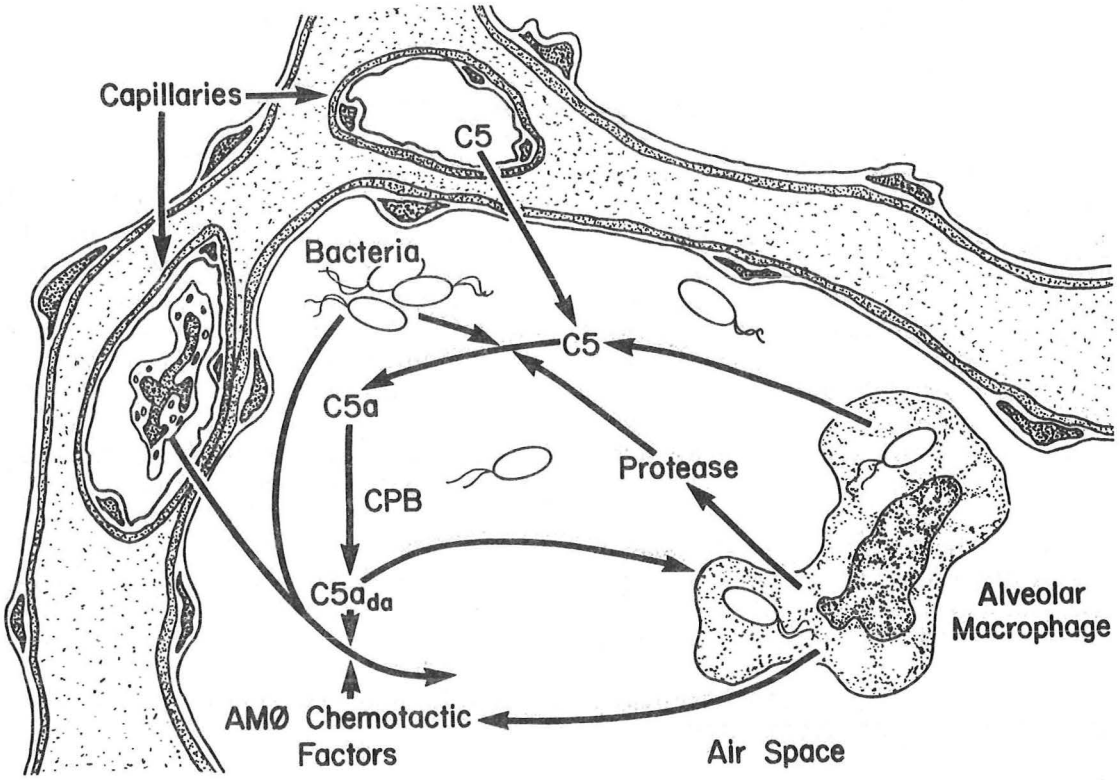
involved in the early recruitment of granulocytes to the lung following bacterial challenges (Table 13). Toews et al. (76) and Larsen et al. (77) have utilized congenic C5 sufficient (C5+) and C5 deficient (C5-) mice to evaluate the role of this molecule in neutrophil recruitment to the alveoli. At 0 hour, comparable small numbers of granulocytes are present in both C5+ and C5- animals. Four hours after a pneumococcal challenge, both C5+ and C5-mice exhibited significant increases in neutrophils but C5+ mice had significantly more neutrophils than were recovered from the C5- mice. An 800 fold increase in neutrophils from that seen at 0 hours was noted in 4 hours in C5+ mice and a 72 fold increase was noted in C5- mice. Similar findings were noted following inocula of *Pseudomonas aeruginosa*. More neutrophils were recruited to the lungs of C5+ animals at 6 and 24 hours. However, by 48 hours, the C5- mice had significantly greater numbers of neutrophils present in their lungs. These studies document that the C5 molecule and its fragments are important neutrophil chemotaxins during the early time period after intrapulmonary challenge with *Streptococcus pneumoniae* and *Pseudomonas aeruginosa*. However, neutrophil recruitment also involves other chemotaxins since both chemotactic activity and neutrophil recruitment are present in C5 deficient mice.

The nature of the chemotactic factor (or factors) involved in granulocyte recruitment is unknown but it is possible that this substance is alveolar macrophage derived chemotactic factor. Recent studies of the role of alveolar macrophages in lung defense have emphasized the capacity of this cell to secrete biologic response modifiers. Alveolar macrophages secrete an alveolar macrophage derived chemotactic factor following phagocytosis of microorganisms (78-80). The chemotactic factor preferentially attracts neutrophils with less chemotactic

activity for monocytes and no apparent activity for eosinophils. Intratracheal injection of the chemotactic factor leads to an increase in neutrophils in bronchoalveolar fluid and in pulmonary tissue sections. These factors have been described in certain disease states and recent data indicate that significant impairment of alveolar macrophage secretion of these factors occurs during glucocorticoid and cyclophosphamide administration (81). Alveolar macrophges have also been shown to secrete certain complement components and recent evidence suggests that glucocorticoids and cyclophosphamide also suppress the synthesis of these important mediators (82). Other secretory activities have only recently been described and are of uncertain importance in the defense of the lung. These include leukotriene B_4, a lipoxygenase pathway metabolide of arachadonic acid (83). Although leukotriene B_4 is a potent chemotactic factor for neutrophils (84) its precise role in modulating antibacterial response in the lung is unknown.

Figure 10

MECHANISMS OF GRANULOCYTE RECUITMENT



A schematic summary of the potential mechanisms of granulocyte recruitment following bacterial challenges is shown in Figure 10. C5 in air spaces, derived from blood or alveolar macrophages, may be cleaved by macrophage or neutrophil derived proteases or by the activation of complement pathways by bacteria. This cleavage would result in the formation of C5a. Removal of the C-terminal arginine from C5a by blood or perhaps an alveolar macrophage derived carboxypeptidase could yield the potent stable chemotaxin C5a des Arg. The C5a des Arg may then

attract neutrophils from the capillary directly or by inducing release of chemotactic factors from the resident alveolar macrophages. Additionally, bacteria present in the alveolus may induce the secretion of alveolar macrophage derived chemotactic factors. Finally, growing bacteria might secrete chemotactic factors which are important in granulocyte recruitment. Clearly each of these proposed mechanisms is critically dependent on the presence and/or influx of controlling factors and inhibitors within the alveolar milieu.

A variety of humoral substances other than complement play a role in defense of the lower respiratory tract. In addition to complement, the immunoglobulins play a prominent role in host defense. Because accurate quantitative analysis of immunogloublin concentrations in the lower respiratory tract is logistically and technically difficult, there is little information to prove that patients with hypogammaglobulinemia have local reductions in these humoral factors (85). However, the increased frequency of respiratory infections in such persons, particularly infections caused by encapsulated bacteria suggests this likelihood. For instance, patients with common variable immunodeficiency syndrome, in which circulating IgG levels are low, experience an increase in respiratory infections (86). There has been an association between increased respiratory infection and selective IgG subclass deficiencies (such as IgG_2 and IgG_4) (87-89). Infections in such persons have often been with encapsulated bacteria which normally require opsonization for phagocytosis. Total serum IgG levels are usually normal in persons with selective IgG subclass deficiencies. Routine quantitative immunoglobulin assays will not detect this as a cause of frequent respiratory illness.

Alveolar lining materials such as surfactant, have been identified as another source of opsonic and bactericidal activity in the lower respiratory tract (90-92). Although data are conflicting, at least in certain conditions such as chronic lung disease and oxygen toxicity, the production of this material by the type II pneumocyte is imparied.

In summary, the complex nature of the respiratory defense apparatus precludes a simplistic approach to our understanding of lung defense mechanisms. There are, however, numerous intrinsic defects in these lung defense mechanisms which make the acquisition of pneumonia more likely. Rapid advances are now being made in our understanding of pulmonary host defense mechanisms and provide optimism that at sometime in the future, the development of clinically feasible means to augment impaired defense activities in the lung might be possible.

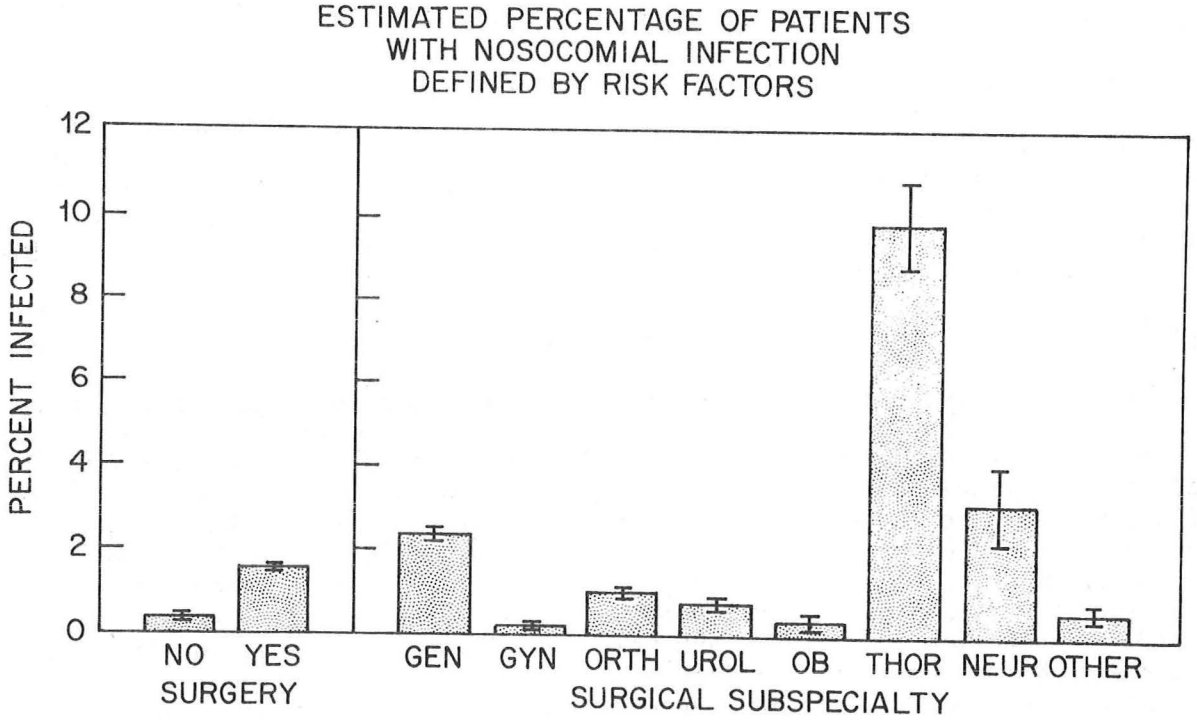
PATIENT RISK FACTORS FOR NOSOCOMIAL PNEUMONIA

For any infectious disease to develop, a potential pathogen must be transmitted to a susceptible host. The nature of the complex interactions among these three determinants of infection are poorly understood but much epidemiologic and clinical research has been devoted to studying the characteristics associated with the occurrence of nosocomial infections. It has not always been clear whether these associations are truly causal, however, and these characteristics are often referred to as risk factors, that is, factors associated with but not necessarily causing infection. Undoubtedly some of these risk factors are true causes of infection; and others are only coincidentally associated with infection because they frequently follow infection or occur along with the truly causal factors. Additionally, two or more risk factors often occur simultaneously in the same patients and might exert additive or even synergistic effects.

Several fundamental concepts are reasonably well accepted. First, if various normal anatomic defense barriers against infection are compromised (urinary or intravenous catheters, endotracheal tubes), even microorganisms considered to be part of the hosts normal or endogenous flora may cause clinical disease (93). Second, the hospital, including its patients, personnel and general environment, provides an excellent ecological reservoir for a multitude of potential pathogenic microorganisms that may be transmitted to patients. Since outpatients who have serious underlying disease, nursing home residents and patients just admitted to the hospital are frequently colonized with gram-negative bacilli it is clear that host factors, not just the hospital environment are important determinants of colonization. Third, the widespread use of antimicrobial agents has led to the development of numerous antibiotic resistent bacteria whose virulence has been documented in numerous recent reports (94, 95). A pointed example of this in our own institution are the numerous infections with methicillin resistent *S. aureus*. Finally, a variety of host factors operating individually and in combination with various quantifiable risk factors characterize certain hospitalized patients who have increased likelihood of colonization with potential pathogenic organisms and increased risk of nosocomial infection.

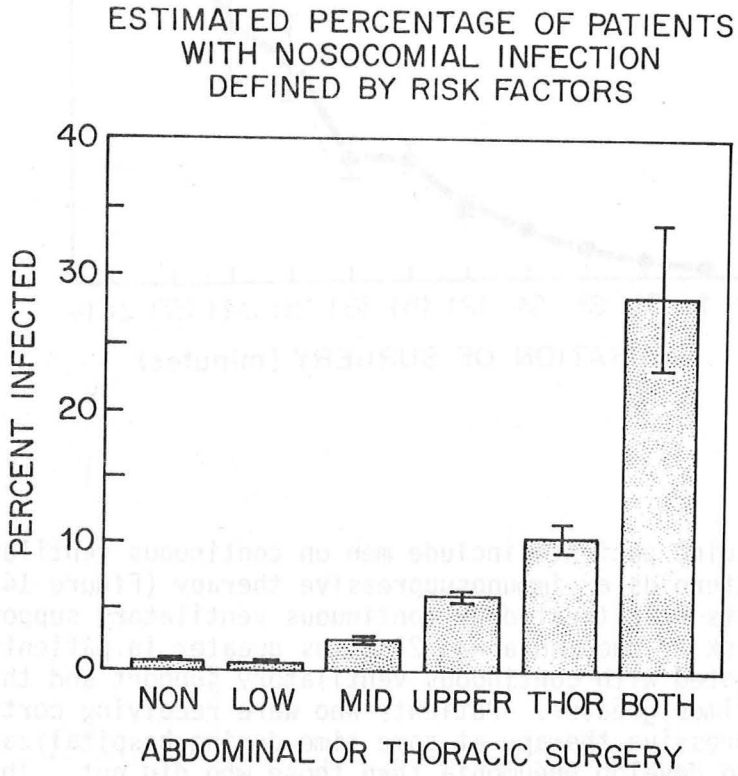
Recent studies utilizing computerized methods of multivariant analysis have characterized the relationships among multiple risk factors and nosocomial respiratory tract infection (11, 96). The majority of nosocomial pneumonias occur on medicine and surgical services (Figure 11). Although surgical patients

Figure 11



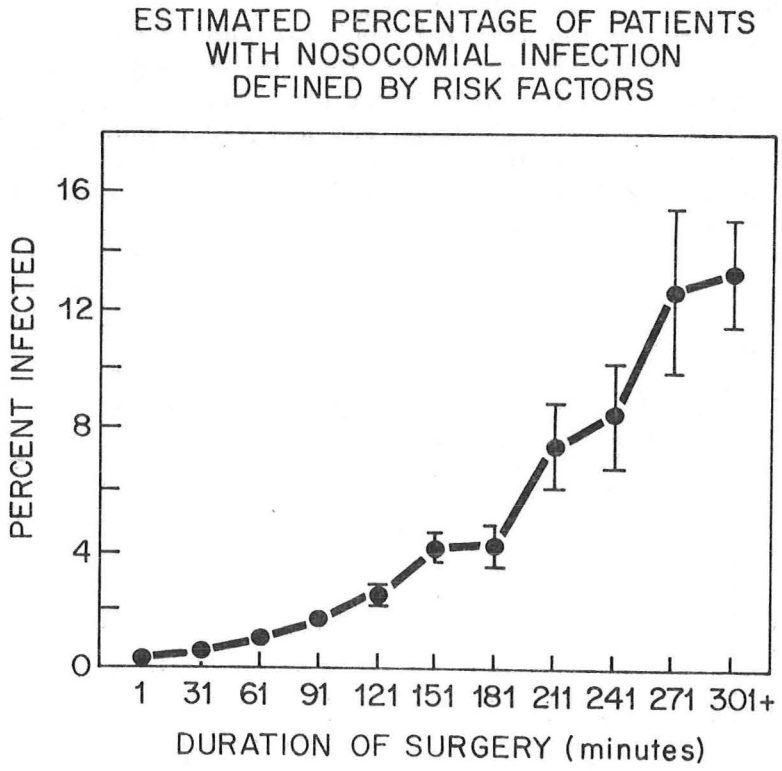
constitute only 42 percent of the target population, they experience 74 percent of all nosocomial pneumonias. Among the surgical subspecialties, pneumonia percentages were highest for thoracic surgery patients, intermediate for general and neurosurgery, and lowest for gynecologic patients and for obstectrical patients undergoing cesarean sections. Surgical patients in the highest risk category included men undergoing combined thoracic -abdominal or mid or upper abdominal surgical procedures (Figure 12). The risk of pneumonia was 38 times greater for combined thoraco-abdominal operations than for those not involving either area, 14 times greater for thoracic and 3.4 times greater for abdominal operations. Upper-abdominal operations were associated with 7.6 times the infection percentage of non-thoraco-abdominal operations and mid-abdominal operations with 3.1 times.

Figure 12



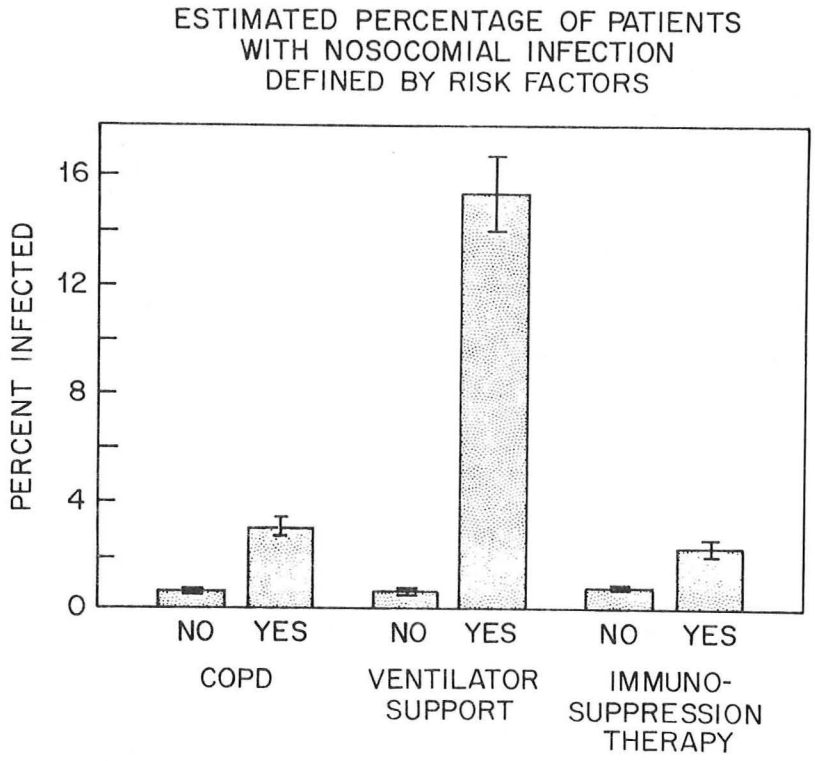
The duration of surgery is also an important risk factor (Figure 13). The percentage of patients with nosocomial pneumonia increased approximately linearly with the duration of surgery, amounting to a 49 fold increase from the lowest to the highest category.

Figure 13



High risk medicine patients include men on continuous ventilatory support and men receiving steroids or immunosuppressive therapy (Figure 14). Approximately 1 percent of patients were treated by continuous ventilatory support on a respirator. The risk of pneumonia was 21 times greater in patients who had been previously treated with continuous ventilatory support and the risk of bacteremia was 16 times greater. Patients who were receiving corticosteroids or other immunosuppressive therapy at some time during hospitalization were 5.3 times more likely to develop pneumonia than those who did not. The presence of chronic obstructive pulmonary disease is also an important predisposing feature.

Figure 14



Data from these studies not only confirmed conclusions of previous investigators as to the significant clinical correlates of nosocomial infection, but provided an important data base that will be useful in trend analysis of infection rates, evaluation of the efficacy of infection surveillance control programs, and research into predictive value of clinical and diagnostic indices of nosocomial infection. Thus major factors that predispose to nosocomial infection are: 1) those that allow microorganisms access to vulnerable areas of the patient (operations, endotracheal tubes), and 2) those that reduce the patient's capacity for resisting the multiplication and injurious effects of microorganisms (immunosuppressive therapy and metabolic sequelea of lengthy operations).

DIAGNOSTIC APPROACH FOR HOSPITAL ACQUIRED PNEUMONIA

The spectrum of specific diseases presenting with fever and new pulmonary infiltrates in the hospitalized patient encompases a multitude of infectious and noninfectious etiologies. The syndrome is common; and mortality, even among appropriately treated cases, runs high. However, effective treatment is available for many of the conditions, in hospitalized patients, particularly those that are immunosuppressed and those with respiratory failure. Pulmonary infiltrates can be caused by a wide variety of noninfectious entities including pulmonary edema, Adult Respiratory Distress Syndrome, neoplasia, hemorrhage, atelectasis, infarction, drugs, radiation, and oxygen toxicity. Recognition of

these noninfectious causes of pulmonary infiltrates may allow these processes to be specifically treated, enabling the patient to avoid the morbidity and mortality of unnecessary diagnostic procedures and unneeded therapeutic agents. Unfortunately, some of the noninfectious processes such as pulmonary hemorrhage or neoplasia can only be recognized conclusively by lung biopsy, and other processes as in the case of drug induced lung disease, can be presumed to be present only after other causes are conclusively excluded.

While the potential for survival often requires early institution of specific therapy, clinical presentation may confound the physician and delay accurate diagnosis. In the setting of acute respiratory failure of various etiologies, the usual clinical indications of pneumonia such as fever, leukocytosis, radiographic infiltrates and the presence of pathogenic bacteria in the respiratory tract secretions are present in patients with or without pneumonia. Thus, an accurate diagnosis of pneumonia is difficult in this setting. Andrews and associates (8) have shown that utilizing the above mentioned criteria frequently leads to misdiagnoses. As shown in Table 14, a majority of patients with and without pneumonia, as determined by postmortem histology, had fever, leukocytosis or leukopenia and pathogens in sputum. While asymmetry on chest X-ray was noted more frequently in patients with histologic pneumonia, this difference was not significant.

Table 14

Correlation of Clinical Findings with Histologic Evidence of Pneumonia

Characteristic	All Patients (n=24), No. (%)	Pneumonia (n=14), No. (%)	Non-Pneumonia (n=10), No. (%)
Fever	22 (92)	14 (100)	8 (80)
Leukocytosis or Leukopenia	22 (92)	14 (100)	8 (80)
Pathogens in Sputum	19 (79)	12 (86)	7 (70)
Asymmetry on Chest Roentgenogram	11 (46)	8 (57)	3 (30)

Andrews, Chest 80:254, 1981

The overall accuracy of the clinical prediction of bacterial pneumonia is shown in Table 15. Sixty-four percent of the cases of histologic pneumonia were correctly diagnosed by review of clinical data whereas 36 percent were thought to have only diffuse lung injury. Eighty percent of the patients with only ARDS were correctly identified clinically, but 20 percent were incorrectly thought to have bacterial pneumonia superimposed on diffuse lung injury. While 29 percent of the patients were misdiagnosed, overall clinical prediction of pneumonia was significantly better than

Table 15

Accuracy of Prediction of Pneumonia
Using Clinical Data

Group	Number	Correctly Diagnosed, No. (%)	Misdiagnosed, No. (%)
Histologic Pneumonia	14	9 (64)	5 (36)
Nonpneumonia	10	8 (80)	2 (20)
Combined	24	17 (71)	7 (29)

Andrews, Chest 80:254, 1981

that which would have occurred by chance alone. Bell and coworkers (97) performed a similar study of 84 patients with the Adult Respiratory Distress Syndrome (Table 16). Forty-seven patients died. Pneumonia was clinically suspected in 21 patients and was found at necropsy in 19, representing a false-positive rate of 10 percent. Pneumonia was not clinically suspected in 26 patients but was shown by histologic evidence in 16, representing a false-negative rate of 62 percent.

In the patient who is suspected of having a nosocomial respiratory infection, knowledge of the host's underlying disease, the associated risk factors, the physical findings, chest radiographic findings and the results of the gram-stain of the screened sputum specimen should provide information on which to base initial empiric antimicrobial therapy (Figure 15).

Table 16

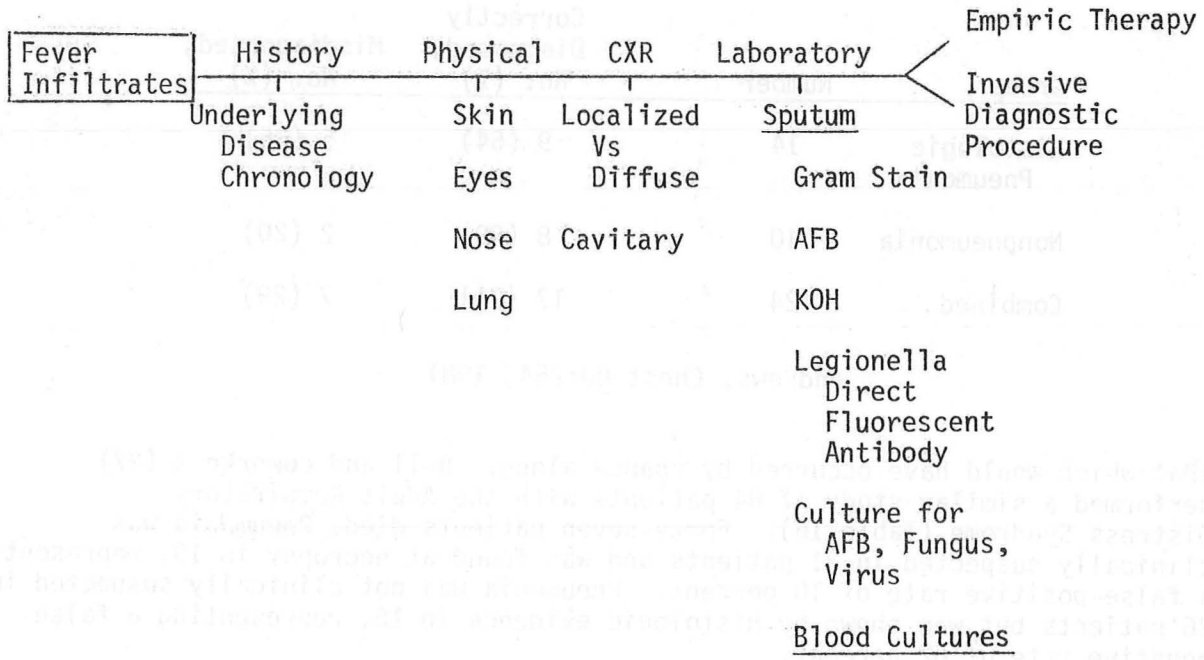
Accuracy of Predicting Pneumonia
Using Clinical Data

		Post Mortem	
Clinical Diagnosis	Number	Pneumonia Present	Pneumonia Absent
Pneumonia	21	19	2
ARDS only	26	16	10

Bell, Ann. Intern. Med. 99:293, 1983

Figure 15

Diagnostic Approach for Hospital Acquired Pneumonia



History

The immunologic defect associated with the underlying disease is an important factor in determining the most likely etiologic agent for a specific patient. Immunosuppressed patients have been divided into categories based on their *in vitro* immunologic lesion alone as a means of predicting likely pathogens. This classic concept of selective impairment of the immune system should be interpreted with some caution. Considerable cross over of immune dysfunction exists among patients with malignant lesions and specific pathogens can differ substantially among immunosuppressed patient populations even when the pattern of *in vitro* studies suggests that their immunologic defects are very similar. None the less, categorication of infections most often associated with impairment of a specific type of immunity is useful in the initial approach to hospitalized patients with fever and infiltrates (Table 17).

Table 17

Type of Immunologic Defect or Related Factor and Associated Microorganisms

Defect or Factor	Microorganism			
	Bacteria	Fungi	Viruses	Parasites
Abnormal T-Lymphocyte Function	Listeria monocytogenes Norcardia Salmonella (species other than typhi) Mycobacteria Legionella	Cryptococcus neoformans Histoplasma capsulatum Coccidioides immitis Trichosporon	Cytomegalovirus Varicella-zoster Herpes simplex	Pneumocystis carinii Toxoplasma gondii Strongyloides stercoralis
Abnormal B-lymphocyte function	Streptococcus pneumoniae Haemophilus influenzae	....	....	....
Neutropenia (<500 neutrophils/mm^3)	Pseudomonas aeruginosa Escherichia coli Klebsiella Serratia Aeromonas Other gram-negative bacilli	Aspergillus Zygomycetes	....	....
Splenectomy	S. pneumoniae H. influenzae E. coli Staphylococcus aureus Neisseria meningitidis	....	....	....
Decreased serum complement	S. pneumoniae H. influenzae Neisseria spp.	....	....	....
Use of corticosteroid therapy equivalent to >20 mg of prednisone daily or cytotoxic therapy (or both)	S. aureus L. monocytogenes Mycobacteria P. aeruginosa Nocardia Other gram-negative bacilli	Aspergillus Zygomycetes H. capsulatum C. neoformans C. immitis	Cytomegalovirus Varicella-zoster Herpes simplex	P. carinii T. gondii Strongyloides stercoralis

Historical information regarding the chronology of the immunosuppressed state is also of importance as shown by studies in renal transplant patients (Table 18) (98). During the first month after renal transplantation, pulmonary infections are usually related to colonization of the posterior pharynx and aspiration, with gram-negative infections being important. Additionally, bacteremia caused by wound sepsis or infection associated with intravascular lines might occur. One to four months after transplantation, CMV, Herpes simplex, Varicella and *Pneumocystis* are common causes of infection. The spectrum of infection changes primarily because immunosuppressive therapy is most intensive during this time. Later in the hospital course, fungal infections such as *Cryptococcus neoformans* occur more commonly.

Table 18

Causes of Pneumonitis After Renal Transplantation

Period after Transplantation		
< 1 Month	1-4 Months	> 4 Months
Aspiration	Cytomegalovirus	Cryptococcus neoformans
Wound Infection or Intravascular Line Colonization	Herpes simplex	P. carinii
	Varicella-zoster	Legionella
	Pneumocystis carinii	
	Aspergillus	
	Zygomycetes	
	Nocardia	
	Mycobacteria	
	Adenovirus	

Physical Exam

Every physician examining a patient with new pulmonary infiltrates is responsible for a careful examination of the skin, eyes, nose, and central nervous system as well as the lungs (Table 19). Cutaneous lesions may suggest bacterial (*Staphylococcus, Pseudomonas, Nocardia)*, fungal *(Aspergillus, Mucor, Cryptococcus, Candida)*, or viral (cytomegalovirus, Herpes simplex, Herpes zoster) dissemination. Scrapings, aspiration or biopsy of cutaneous lesions should be pursued with appropriate stains and cultures of the samples. Fundiscopic examination may give a clue to dissmeinated fungal or viral infection and inspection of the nares may reveal ulceration suggestive of *Aspergillus* or rhino-cerebral *Mucor*.

Table 19

Causes of Pulmonary Infiltrates in Immunocompromised Patients with Various Conditions

Conditions	Bacteria	Fungi	Viruses	Parasites
Cutaneous Lesions	Staphylococcus aureus Pseudomonas aeruginosa Aeromonas hydrophila Nocardia Mycobacteria Vibrio alginolyticus	Cryptococcus neoformans Blastomyces dermatitidis Aspergillus Coccidioides immitis Zygomycetes Trichosporon	Varicella-zoster Herpes simplex	....
Infections of the Central Nervous System	Streptococcus pneumonia S. aureus Nocardia P. aeruginosa Mycobacteria Legionella Haemophilus influenzae Neisseria	C. neoformans Zygomycetes Aspergillus C. immitis	Varicella-zoster Herpes simplex Cytomegalovirus (Retinal Lesions)	Toxoplasma gondii Strongyloides stercoralis

A discussion concerning signs and symptoms associated with all specific conditions which can mimic nosocomial pneumonia is obviously beyond the scope of this discussion. One pathologic process that should be emphasized is pulmonary edema. Patients who have undergone cardiac or renal transplantation may have fever related to organ rejection and pulmonary infiltrates as a result of interstitial edema due to decreased performance of the transplant organ. The physician should always carefully examine any hospitalized patient for signs of fluid overload and compare current and prior body weights. If one is still uncertain regarding the presence of heart failure, measurement of pulmonary capillary wedge pressure might be diagnostic.

Radiology

The radiographic pattern is helpful in suggesting which etiologic agents are most likely to be involved (Table 20). The differential diagnosis of lobar infiltrates should focus on bacterial pathogens such as gram-negative rods, *Staphylococcus aureus* or *Legionella*. Wedge shaped pleural based processes should suggest *Aspergillus* or gram-negative bacilli. Fungal disease, *Nocardia* and *Pneumocystis carinii* can uncommonly present with focal infiltrates. Diffuse infiltrates involving all lobes bilaterally, in contrast, would suggest viral agents particularly adenovirus or cytomegalovirus or *Pneumocystis*. In one third to one half of patients, diffuse infiltrates will be found to be secondary to nonspecific interstitial pneumonitis (99-100). On rare occasions,

bacteria, fungi, *Legionella* and mycoplasma can produce a diffuse pattern. The description of the type of diffuse infiltrate is less helpful as many infectious agents can cause either interstitial or alveolar processes and many interstitial processes progress to alveolar consolidation patterns as they worsen.

Table 20

Causes of Pneumonia Associated with Diffuse and Focal Infiltrates

Diffuse Infiltrate	Focal (or Cavitary) Infiltrate
Common:	Common:
Cytomegalovirus	Gram-Negative Rods
Pneumocystis carinii	Staphylococcus aureus
Drug Reaction	Aspergillus
Nonspecific Interstitial Pneumonitis	Malignancy
	Nonspecific Interstitial Pneumonitis
Uncommon:	Uncommon:
Bacteria	Cryptococcus
Aspergillus	Nocardia
Cryptococcus	Mucor
Malignancy	Pneumocystis carinii
Radiation Pneumonitis	Tuberculosis
Leukoagglutinin Reaction	?Legionella pneumophilla

Laboratory

Collection of sputum, whether spontaneously produced or induced with a bronchial irritant, for staining and culture should be encouraged in any hospitalized patient with a cough or chest roentgenographic abnormality regardless of immune status. The results of aerobic bacterial and fungal cultures from specimens collected by using any of these methods must, however, be interpreted with considerable caution. As previously mentioned, the orpharynx and upper respiratory tract of many hospitalized patients are colonized with gram-negative aerobic bacteria, *S. aureus*, *Candida* and ocassionally saprophytic fungi such as *Aspergillus* and rarely *Cryptococcus neoformans*, *Nocardia* or atypical mycobacteria. Cytomegalovirus or herpes virus may be present with or without oropharyngeal disease and may contaminate pulmonary viral cultures. Because these organisms contaminate the sputum as it passes through the oropharynx, the validity of subsequent cultural isolates is questionable.

For direct examination of sputum, a Gram stain should be performed. If few squamous epithelial cells (fewer than 10 per low power field) or many polymorphonuclear leukocytes (more than 25 per low power field) or both are seen, the specimen most likely is expectorated sputum and not saliva (101). The physician should remember, however, that in the hospitalized patient who is severely neutropenic but able to produce sputum, few or no polymorphonuclear leukocytes will be observed on a Gram stain. Generally such patients produce

little or no sputum. A negative Gram stain does not rule out bacterial pneumonia nor does a positive Gram stain specifically indicate the diagnosis of bacterial pneumonia. The presence of many bacteria with similar morphologic features may suggest a specific bacterial pathogen.

If available, expectorated sputum should be studied with several stains in addition to the usual Gram and acid-fast stains. Wet mount potassium hydroxide preparation should be performed when fungal infections are a consideration and methenamine silver nitrate stain should be done if pneumocystis is likely. In certain cases, the direct fluorescent antibody stain for *Legionella pneumophilla* should be applied and may be positive in a third of all cases eventually proven by culture (102).

Sputum cultures may eventually yield the following organisms which would always be considered pathogenic: *Legionella* species, *M. tuberculosis* and dimorphic fungi (*H. capsulatim, B. dermatiditis, C. immitis* and *Sporothrix schenkii*). However, because of the usually urgent need for prompt diagnosis, cultures of these organisms are seldom of value in clinical management. As shown in Table 21, the isolation of many pathogens entails days to weeks. Further, as previously mentioned,the isolation of *C. neoformans, Nocardia* or atypical mycobacteria from sputum may result from colonization of the oropharyngeal airway and thus not indicate the presence of an infection. Blood cultures for bacteria and fungi are always obtained as part of the laboratory evaluation in these patients.

Table 21

Time Intervals necessary for Preliminary Identification of Selected Opportunistic Organisms from Cultures of Tissue or Fluid Specimens

Organisms	Interval
Legionella spp	3 days to 10 days
Nocardia asteroides	5 days to 4 wk
Mycobacterium Tuberculosis	2 to 8 wk
M. avium-intracellulare complex	3 to 8 wk
Aspergillus spp.	1 to 5 days
Zygomycetes spp	1 day to 2 wk
Blastomyces dermatitidis	4 days to 4 wk
Coccidioides immitis	3 days to 4 wk
Cryptococcus neoformans	4 days to 6 wk
Histoplasma capsulatum	5 days to 6 wk
Sporothrix schenckii	4 days to 1 wk
Chlamydia trachomatis	2 to 3 days
Cytomegalovirus	< 24 hours with use of monoclonal antibody fluorescence technique 5 days to 3 wk with use of conventional cell culture technique

Despite a vigorous evaluation, traditional methods to determine the etiology of a pneumonia often fail in the hospitalized patient. This is particularly true in the setting of diffuse bilateral disease. In one series of 80 immunosuppressed patients with diffuse pulmonary infiltrates studied prospectively, an etiologic diagnosis was made by sputum and blood cultures alone in only 4 cases (5%) and suspected on the basis of serology in another 4 cases (103). If this initial evaluation is inconclusive, the clinician is faced with 3 options: 1) watch, wait and reevaluate, the presumption being that the patient does not have a lower respiratory tract infection; 2) initiate empiric antimicrobial therapy, the presumption being that the patient has an infectious cause for his infiltrate; or 3) obtain additional specimens to aid diagnosis and base therapeutic decisions on the results obtained. The first option is dangerous, particularly in a critically ill or immunocompromised host where even brief delay in initiating appropriate antimicrobial therapy may lead to a fatal outcome. Thus, most clinicians elect to follow option 2 or 3. Some prefer to institute appropriate empiric therapy, watch carefully for clinical improvement and, seeing none within 48 hours, proceed to invasive diagnostic tests. Others prefer to obtain additional specimens prior to initiating therapy. There has been no adequate study comparing outcome of empiric versus specific therapy in a defined patient group. Thus, we lack data to help address this clinical question. It is not clear that therapy based on results of a particular diagnostic procedure, combination of procedures or sequence of procedures influences outcome in patients with nosocomial respiratory infections. Thus, the clinician must consider the morbidity and mortality of the diagnostic procedure for the patient, the toxic effects of the drug therapy, and his ability to manage complications later if he lacks unequivocal, certain knowledge of the diagnosis.

INVASIVE DIAGNOSTIC PROCEDURES

The following invasive procedures may be used in the diagnosis of nosocomial respiratory infection: transtracheal aspiration, percutaneous lung aspiration, fiberoptic bronchoscopy with transbronchial biopsy, protected bacteriological specimen brush or bronchoalveolar lavage, or open lung biopsy. Each of these invasive procedures will be briefly reviewed.

Transtracheal Needle Aspiration

Whether transtracheal aspiration should be performed to obtain an adequate sputum specimen for stains and a noncontaminated culture is controversial. Some physicians are enthusiastic about the yield and safety of this technique (104, 105). However, when all microbes are considered, the yield and expedience of diagnosis by transtracheal needle aspiration parallel those of spontaneous or induced sputum collection. Additionally, severe complications, especially prolonged hemorrhage in thrombocytopenic patients has been reported. Finally, because numerous patients in whom this procedure would be contemplated are on the ventilator and are thus, not candidates for transtracheal needle aspiration, this procedure is not being used in our institution.

Percutaneous Needle Aspiration

Percutaneous needle aspiration, performed with an 18 gauge, thin walled spinal needle, can provide uncontaminated material from lung parenchyma for microbiologic and cytologic examination. This procedure has been used extensively

in the management of heart transplant patients and in pediatric cases. A compilation of several series is shown in Table 22 (106-109). Disadvantages of this procedure are the frequent complications (pneumothorax and hemorrhage) and the limitation of sampling to peripheral lung tissue. In most series of percutaneous needle aspiration, the complication rates exceed those for both bronchoscopic biopsy and open lung biopsy procedures. In general, needle aspiration has its highest yield in localized or cavitary peripheral lung lesions.

Table 22

Role of Needle Aspiration for Diagnosis of Pulmonary Infiltrates in Immunocompromised Patients

Author	No.	Comments	Specific Etiologic Diagnosis (%)	Complications (%) Pneumothorax	Hemorrhage
Bandt	25	Miscellaneous Infiltrates	76	12	8
Costellino	108	Focal Infiltrates	73	26	3
Zavala	11	Miscellaneous Infiltrates	55	9	18
Greenman	34	Miscellaneous Infiltrates	35	9	9

Bandt, JAMA 220:1578, 1972
Costellino, Radiology 132:563, 1979
Zavala, Am. Rev. Respir. Dis. 123:125, 1981
Greenman, Am. J. Med. 59:488, 1975

Fiberoptic Bronchoscopy

Transbronchial biopsy: Several series have now reported the diagnostic yield of fiberoptic bronchoscopy with transbronchial forceps biopsy in immunocompromised patients with new pulmonary infiltrates (110-115). This procedure offers the advantage of providing lung parenchyma for histologic examination while avoiding open thoracotomy. Its disadvantage is that only small fragments (1-1.5 mm in diameter) each of which contains approximately 25 alveolar spaces are obtained, creating the possibility of sampling error and false-negatives. The compilation of diagnostic results and complication rates is depicted in Table 23. The diagnostic accuracy of transbronchial biopsy varies considerably depending on the nature of the pulmonary lesion, technical expertise of the bronchoscopist, method of handling the specimen and the experience of the pathologist in dealing with small pieces of tissue. Diagnostic information is provided in approximately 40-50 percent of acute pulmonary infiltrates, though the yield may be as high as 80 percent when the prevalence of infectious diseases is high, 3-5 pieces of lung tissue are obtained, and the specimen is vigorously evaluated. Nonspecific interstitial pneumonitis may be found in nearly half the cases, and the frequency with which such nonspecific biopsies will be falsely negative for infection or other specific etiologies has been reported variously as 20 percent (115) to as high as 50 percent (112).

Table 23

Role of Transbronchial Biopsy in
Diagnosis of Pulmonary Infiltrates in
Immunocompromised Patients

Author	No.	Comments	Specific Etiologic Diagnosis (%)	Complications (%) Pneumothorax	Hemorrhage
Nishio	47	Miscellaneous Infiltrates	30	4	4
Feldman	39	Miscellaneous Infiltrates	45	11	0
Poe	35	Miscellaneous Infiltrates	46	19	26
Cunningham	31	Miscellaneous Infiltrates	48	0	6
Lauver	24	Miscellaneous Infiltrates	59	7	7
Matthay	25	Miscellaneous Infiltrates	84	8	8

Nishio, Am. Rev. Resp. Dis. 121:307, 1980
Feldman, JAMA 238:1377, 1977
Poe, Am. Rev. Resp. Dis. 119:25, 1979
Cunningham, Am. Rev. Resp. Dis. 115:213, 1977
Lauver, Am. J. Med. 66:580, 1979
Matthay, Thorax 32:539, 1977

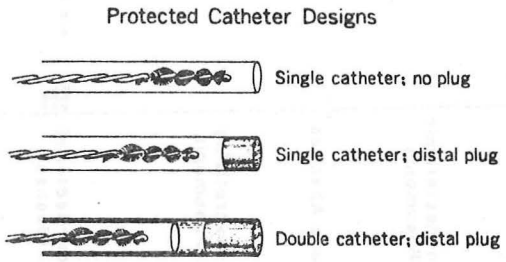
The most common complications with transbronchial biopsy are pneumothorax or hemorrhage. Restricting analysis to studies of immunocompromised hosts,the incidence of pneumothorax ranges from 0 (111) to 19 percent (115). The incidence of significant hemoptysis is about 7 percent. Significant is arbitrarily defined as 25 ml or more of grossly bloody sputum. Fatal hemorrhage has been reported (113) and severe bleeding is most common in the presence of uremia or a bleeding diathesis due to leukemia or a cancer chemotherapy (111). Those unsuitable for this procedure include the uncooperative patient or one with uncorrectable hypoxemia or a bleeding disorder (platelet count less than 50,000 per cu mm after platelet transfusion, BUN > 50 and prolonged prothrombin time).

Conventional bacteria such as staphylococcus and gram-negative bacilli may be recovered from cultures of transbronchial biopsies. However, interpretation of cultures is complicated due to contamination of the specimen during passage through the inner port of the instrument. Alternate methods must be utilized to detect the usual bacterial agents such as a transthoracic aspirate or a protected bacteriologic brush.

Protected Bacteriologic Brush

Brushings through the fiberoptic bronchoscope when combined with transbronchial biopsy are complimentary and may increase overall yield. As previously mentioned, routine bacteriologic cultures are not reliable because of contamination of the bronchoscope channel with oropharyngeal and nasopharyngeal bacteria. Recently, however, special telescoping catheters with distal plugs have been devised to allow a sterile sampling for routine bacteria in the lower respiratory tract. Numerous catheter designs have been utilized but sensitivity and specificity were superior for a double catheter with a distal plug (Figure 16).

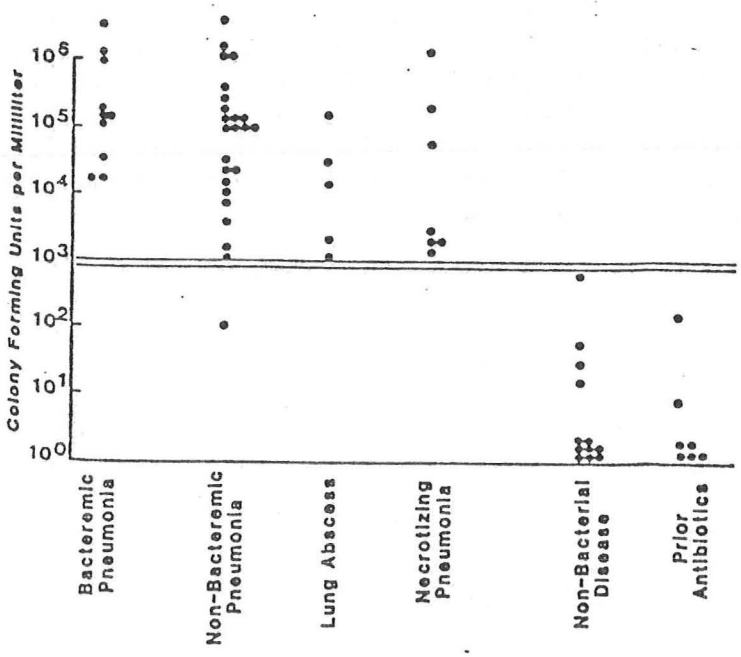
Figure 16



Methodologic details are very important to insure reliable results with the protected bacteriologic brush. Aerosol anesthesia with 15 ml of 2-4 percent lidocaine is performed because the injection of fluid through the inner channel of the bronchoscope washes large numbers of oropharyngeal bacteria into the lower airways. Upper airway secretions are not suctioned into the inner channel of the bronchscope prior to collecting the brush specimen. After the bronchoscope is positioned as close to the infiltrate as possible, the outer and then the inner catheters are extended for a total distance of 3-4 cm beyond the bronchoscope prior to advancing the brush from the inner catheter to avoid pooled secretions at the instrument tip. Following the brushing procedure, the brush is completely withdrawn into both catheters before removal. Following removal from the bronchoscope, the distal portion of the inner catheter is wiped clean with 70 percent alcohol and the distal inner catheter and finally the protected brush are severed with sterile instruments. A system for quantitative bacterial cultures is mandatory since low concentrations of contaminants are frequently recovered following brushing, making qualitative bacteriology uninterpretable. Serial 10 fold dilutions are then performed so the number of bacteria present can be quantitated.

Figure 17

QUANTITATIVE CULTURE RESULTS
WITH PROTECTED BRUSH CATHETER



Wimberley, Chest 81:5, 1982

Figure 17 summarizes the quantitative culture results from a series of 65 patients (116). With one exception, the 46 patients with diagnoses of bacterial lung disease who had not received antibiotics had protected catheter isolates with colony counts greater than 10^3 colony forming units (CFU) per ml. Conversely, all patients with nonbacterial lung disease and those who had received antibiotics prior to the procedure had colony counts of less than 10^3. One patient with a clinical diagnosis of pneumonia had bacteria present in low concentrations only. It should be noted that those patients who were believed to have pneumonia but who had received prior antibiotics all had catheter counts of less than 10^3 CFU per ml, suggesting that the usefulness of this brush might be limited in patients who have received antibiotics.

If the considerable methodologic considerations can be overcome, data from studies in primates and patients show that the protected bacteriologic brush technique is both sensitive and specific in diagnosing lower respiratory tract infection (Table 24)(116-119).

Table 24

Plugged Telescoping Catheter: Compiled Results

	True Positive	False Positive	True Negative	False Negative
Wimberley ARRD 119:337	4	0	8	0
Wimberley Chest 81:556	40	0	12	1
Higuchi ARRD 125:53	7	1	9	3
Hayes ARRD 122:319	-	0	10	-
TOTAL	51	1	39	4

Bronchoalveolar Lavage

Bronchoalveolar lavage through the fiberoptic bronchoscope should be performed whenever a bronchoscopic procedure is performed as this procedure is complimentary to a transbronchial biopsy and may increase the overall yield. Bronchoalveolar lavage has been shown to be a sensitive technique for the diagnosis of *Pneumocystis carinii* in patients with AIDS (120). A recent study has shown the usefulness of bronchoalveolar lavage in the diagnosis of pulmonary infiltrates in the non-AIDS immunosuppressed patient (121). Overall, lavage alone was used to reach a diagnosis in 61 of 92 cases, for a sensitivity of 66 percent. No complications were noted. The highest yields were for opportunistic infections, and the lowest, for pulmonary malignancy and drug toxicity.

Cytologic examination of bronchoalveolar lavage for *P. carinii* pneumonia had a yield of 82 percent (Table 25). Lavage was also successful in identifying cytomegalovirus pneumonia in 10 of 12 cases (83%). Diagnoses were made quickly by observing the cytopathologic changes seen in lavage fluid in some cases. In other cases, however, the diagnosis was made from culture of lavage fluid which took 5 to 10 days. The utilization of immunofluorescent staining of lavage fluid with a monoclonal antibody specific for cytomegalovirus might have made quicker diagnosis possible (122). The detection rate for fungal disease by bronchoalveolar lavage was 83 percent. Although no false positive results were found in this small number of cases, the problem of differentiating colonization from tissue invasion remains, especially with such organisms as *Aspergillus, Cryptococcus* and *Candida*. Four of five cases of mycobacterial

disease were diagnosed from lavage fluid cultures (80%). Granulomas generally were not seen with biopsies and the use of transbronchial biopsy did not increase the yield for diagnosing mycobacterial disease. It should be noted, however, that because organisms were not usually seen on stain of lavage samples, cultures were needed to make a diagnosis which required several weeks. In summary, bronchoalveolar lavage is a safe, easy and valuable procedure for use in immunosuppressed patients with diffuse pulmonary infiltrates. The technique can be used in thrombocytopenic patients and those requiring ventilatory support if adequate oxygenation can be achieved. Highest yields are obtained in diagnosing opportunistic infection but it should be noted the high yield in this study was dependent on cultural diagnoses in a significant number of cases. Rapid diagnoses of pathogens was not always possible.

Table 25

Diagnostic Sensitivity of Bronchoscopic Procedures in Non-Aids Immunosuppressed Patients

Diagnosis	Bronchoalveolar Lavage	Transbronchial Biopsy	Bronchial Washings or Brushings	Total Yield All Procedures
	n Positive/n Tested (%)			
Pneumocystis carinii Pneumonia	18/22 (82)	11/12 (92)	7/19 (37)	21/22 (95)
Viral Pneumonia	10/12 (85)	3/6 (50)	5/12 (42)	11/12 (92)
Fungal Pneumonia	5/6 (83)	0/2	3/6 (50)	5/6 (83)
Mycobacterial Disease	4/5 (80)	1/5 (20)	4/5 (80)	5/5
Bacterial Pneumonia	1/1	0/1	0/1	1/1
Malignancy	10/22 (46)	9/16 (56)	12/22 (55)	14/22 (64)
Drug Toxicity	6/15 (40)	12/15 (80)	6/15 (40)	12/15 (96)

Stover, Ann. Intern. Med. 101:1, 1984

Based on the statistics in Tables 23-25, I favor taking samples via the fiberoptic bronchoscope as a diagnostic procedure prior to open lung biopsy in most patients unless the patient has a bleeding diathesis, cannot oxygenate adequately while the bronchoscope is obstructing the airway, or is deteriorating so rapidly that it seems likely that only one procedure will be tolerated by the patient. In these cases, the performance of an open lung biopsy is preferred. Transbronchoscopic specimens can be fixed and stained within 3-4

hours using modern techniques and thus an open lung biopsy could be done in the same day as bronchoscopy if the latter procedure does not provide a diagnosis.

Open Lung Biopsy

The diagnostic accuracy of open lung biopsy is shown in Table 26 (103, 106, 123-126). Open lung biopsy is viewed by most as the definitive procedure for premortem diagnosis. Modern surgical technique employs a "limited thoracotomy" without rib resection. In this high risk, often critically ill population, complications remain remarkably low, with delayed pneumothorax and prolonged ventilatory assistance being the most common. Operative mortality is less than 5 percent and can in part be avoided by not delaying the operative procedure until the patient is moribund. The diagnosis established by lung biopsy can be expected to lead to a change in therapy in as many as one half of patients (123). Given the lethality of the underlying disease in this population and the virulence of the pulmonary infections, it is not surprising that identifying a specific etiology does not guarantee improved survival. Some authors have reported that those patients in whom open lung biopsy has yielded a specific diagnosis fared no better than those without diagnosis (123). These data are similar to that from bronchoscopic studies performed by Pennington et al. (127). However, in establishing a specific diagnosis, patient management may be made more rational. In some patients a specific early diagnosis leads to life saving therapy (103, 128, 129) while in others potentially toxic empiric therapy might be discontinued when infection is ruled out by lung biopsy.

Table 26

Role of Open Lung Biopsy for Diagnosis of Pulmonary Infiltrates in Immunocompromised Patients

Author	No.	Comments	Specific Etiologic Diagnosis (%)	Hemorrhage
Rossiter	83	Miscellaneous Infiltrates	55	0
Singer	44	Miscellaneous Infiltrates	61	0
Greenman	48	Miscellaneous Infiltrates	65	1
Leight	42	Miscellaneous Infiltrates	71	0
Wolff	24	All Children	88	0
Rosen	47	Miscellaneous Infiltrates	91	0

Rossiter, J. Thorac. Cardiovasc. Surg. 77:338, 1979
Sanger, Am. J. Med. 66:110, 1979
Greenman, Am. J. Med. 59:488, 1975
Leight, Chest 73:477, 1978
Wolff, Pediatrics 60:41, 1977
Rosen, Am. J. Med. 58:794, 1975

TREATMENT OF HOSPITAL-ACQUIRED PNEUMONIA

> Nature has provided, in the white corpuscles as you call them - in the phagocytes as we call them - a natural means of devouring and destroying all disease germs. There is at bottom only one genuinely scientific treatment for all diseases and that is to stimulate the phagocytes...Drugs are a delusion. If the phagocytes are stimulated they devour the disease; and the patient recovers--unless of course he's too far gone.
>
> George Bernard Shaw
> Act I
> *The Doctor's Dilemma*
> 1906

Therapy for pneumonia in the hospitalized patient requires attention to insuring adequate ventilation and oxygenation, identifying the etiologic agent, and providing adequate antimicrobial therapy. A decision whether to treat the patient empirically with broad spectrum therapy, thus sparing the patient the risks of a diagnostic procedure or specifically after biopsy requires considerable judgment rather than guidelines that can be methodically listed. Each patient and each underlying disease category must be considered separately rather than an attempt being made to develop a uniform strategy for all hospital-acquired pneumonias. There has been no adequate study comparing outcome of empiric versus specific therapy in a defined patient group. There have been no prospective, well controlled, comparative studies of therapeutic antimicrobial regimens for gram-negative pneumonia occurring in critically ill patients. Furthermore, no investigators have separated bacteremic and nonbacteremic respiratory infections and demonstrated the superiority of one regimen over another in a randomized trial.

An organized approach to the immunocompromised host with fever and new lung infiltrates depends on an appropriately weighted differential diagnosis. Two major considerations should allow the clinician to narrow the list of etiologic possibilities for a specific patient. The first is the underlying disease process and the risk factors attendant upon it and its therapy (Table 17). The second is the radiographic pattern of the new lung infiltrate (Table 20). With these considerations in mind, plus the noninvasive work up recommended above, some patients can be successfully managed without an invasive procedure. However, in many instances no specific etiology is discovered after noninvasive or invasive diagnostic procedures and the patient must be treated empirically.

Gram-Negative Pneumonia

The most common bacterial pathogens isolated from hospital patients whose fever is treated empirically with antibiotics are *E. coli*, *S. aureua*, *Klebsiella* species and *P. aeruginosa*. Obviously, any antimicrobial regimen used empirically in hospitalized patients should offer adequate coverage against the most frequently isolated bacterial pathogens. Historical comparisons, such as those undertaken by Waldvogel (130) suggest

that the best results in treating gram-negative bacillary pneumonia have been obtained from the use of two appropriate agents, usually an aminoglycoside combined with a beta-lactam agent.

The data supporting the initial routine use of multiple antibiotics in gram-negative pneumonia comes largely from studies of the treatment of gram-negative infections in neutropenic patients. The reason for this apparent advantage of multiple antibiotics is uncertain. The term "synergism" is commonly used to describe the interaction of two microbial agents (or occasionally more than two) in which the effect produced by the drugs in combination is greater than their individual effect. Additive effects, particularly those when two agents are given at staggered intervals may result in more sustained blood and tissue antibacterial activity. The putative advantage of combination therapy may be that different drugs are excerting their activities at different times and giving better round the clock antibacterial coverage. Additionally, other arguments for the use of combinations include prevention of the emergence of resistance and the advantage of dealing with mixed infections.

Whatever the mechanism, clinical studies have shown that patients with cancer and gram-negative bacillary infection have a favorable outcome significantly more often when given synergistic combinations of antibiotics than when given nonsynergistic or antagonistic combinations. A review of 12 controlled trials of therapy with single versus multiple antibiotics and with synergistic versus nonsynergistic combinations of antibiotics in neutropenic patients infected with gram-negative bacilli is shown in Table 27 (131). Multiple antibiotics were more effective than single antibiotics and synergistic combinations were more effective than nonsynergistic combinations. Thus, for most patients with nosocomial pneumonia, combination antibiotic therapy remains the standard empiric therapy.

Table 27

Summary

Single Vs. Multiple Antibiotics
in Neutropenic Patients Infected
With Gram-Negative Bacilli

Type of Therapy	Number	% with Clinical Response
Single Antibiotic	195	61
Multiple Antibiotics	170	81
Nonsynergistic Combinations	179	43
Synergistic Combinations	208	76

Klastersky, Rev. Infect. Dis. 5(Suppl):S21, 1983

During the 1970s, a large number of clinical trials evaluated various two or three drug combinations in empiric management of febrile granulocytopenic cancer patients. A representative study which evaluated large numbers of patients is shown in Table 28 (131). For the most part, no particular combination was shown to be uniquely superior. Indeed the strongest recommendations that can be offered from these cumulative data would include the following. First the drug regimen used at a particular center should focus on the predominant pathogens at that institution, and should take into account the cost of the drugs and the experience of the staff. Second, if an aminoglycoside is included in the regimen, serial monitoring of drug levels in the blood is an essential aspect of the management, both to assure efficacy as well as to minimize potential nephrotoxicity and ototoxicity. Third, whatever the specific regimen, it should be employed promptly and in a standardized manner whenever a granulocytopenic patient becomes febrile.

Table 28

Clinical Response to Empiric Therapy
in Febrile Neutropenic Patients

Combination	Number	% Response in Culture Documented Infections	% With Nephrotoxicity
Carbenicillin Plus Gentamicin	107	66	2
Cephalothin Plus Gentamicin	102	58	12
Cephalothin Plus Carbenicillin	85	58	4
Carbenicillin Plus Amikacin	98	62	6
Carbenicillin Plus Cefazolin Plus Amikacin	102	70	7

Klastersky, Rev. Infect. Dis. 5(Suppl):S21, 1983

There has been much speculation about the factors responsible for the poor results of therapy in gram-negative pneumonia. Besides underlying disease, most antibacterial agents poorly penetrate respiratory secretions (132, 133). A comprehensive review of this subject by Pennington (132) attempted to relate serum concentrations of antibiotics with concentrations measured in bronchial secretions or sputum. Penicillin levels measured in secretions varied between 5 and 20 percent of the serum levels. Sputum levels of tetracycline ranged between 1 and 60 percent. Sputum erythromycin levels were only 5 percent of measured blood levels while sputum aminoglycoside levels varied between 25 and 67 percent of serum values. The latter is particularly important since serum

levels are often close to minimal inhibitory concentrations for many important pathogens. Thus, limited diffusion of drugs into infected lung tissue and secretions could be a major factor in limiting therapeutic success. However, the concept that sputum or bronchial levels of antimicrobial agents are important determinants of outcome is unproven. There is no definite evidence that drug levels in sputum bear any relation to clinical response to treatment in chronic or severe tracheobronchial infections (134).

Another factor that may militate against therapeutic success is that conditions in the tracheobronchial tree are not optimal for the activity of some important antibiotics. This factor is most obvious for aminoglycoside therapy. Aminoglycosides have markedly attenuated activity at acid pH, and there may be 100 fold difference in *in vitro* activity between pH 6.5 and pH 8.5 (135). Respiratory secretions have a pH in the acid range. Bronchoscopy of normal persons revealed a mean endobronchial pH of 6.58 which was not significantly different from the pH obtained on bronchoscopy of persons with pneumonia (pH 6.48). This could be one explanation for the questionable efficacy of aminoglycosides when used alone for gram-negative pneumonia. In contrast, the activity of both penicillin and cephalosporin is not affected by wide ranges of pH.

New Antimicrobial Agents

During the last several years, a number of new beta-lactam antibiotics have been introduced to the drug arena, including the third-generation cephalosporins, the ureido-penicillins, the piperazine-penicillins and the carbapenems. The unique features of these agents elicit new options and considerations for the treatment of hospital acquired pneumonias. For example, the third-generation cephalosporins (cefotaxime, moxalactam, ceftizoxime, cefoperazone and ceftazidime) share a broad spectrum of activity that includes the Enterobacteriaceae, some Pseudomonads (particularly in the case of ceftazidime and cefoperazone), many gram-positive isolates and some anaerobes. However, none of the drugs are effective against the enterococci, Listeria, or methicillin resistant *S. aureus*. The third-generation cephalosporins have a longer serum half-life than did earlier generations of cephalosporins so the former can be administered on a less frequent dosage schedule. Furthermore, the peak serum level of these drugs well exceeds the minimal inhibitory concentrations of most of the major pathogens. Of particular interest, certain of these agents, when used as monotherapy (cefoperazone, ceftazidime) have shown serum bactericidal levels exceeding those obtained with standard "synergistic" combinations. Thus, these drugs, as a class appear to possess a number of unique attributes: a broad spectrum of activity; ability to achieve high serum bactericidal levels; good tissue penetration; and a low level of toxicity.

Table 29

Summary of Cefoperazone Trials in Lower Respiratory Tract Infection

Pathogen	Bacteriologic Response/Episodes Satisfactory	Clinical Response/Episodes Satisfactory
	Number (Percent)	
Staphylococcus aureus	18 (83)	19 (95)
Hemophilus influenzae	25 (100)	27 (100)
Pseudomonas aeruginosa	16 (43)	17 (82)
Other Gram-Negative Pathogens	46 (85)	46 (94)

Gardner, Rev. Infect. Dis. 5:5137, 1983

The carbapenems (imipenem), a new class of beta-lactams, have the broadest spectrum of all the newer antibiotics. Susceptible organisms include not only Enterobacteriaceae, but also *P. aeruginosa*, gram-positive bacteria (*S. aureus*, coagulase-negative staphylococci and enterococci), and anaerobes (including *Bacteroides fragilis*). The carbapenems are inactive against methicillin-resistant *S. aureus* and the non-aeruginosa strains of pseudomonas (*P. cepacia* and *P. maltophilia*). As with other beta-lactams, imipenem has shown minimal toxicity in early clinical trials.

In summary, the recent antibiotic developments have provided the clinician with a number of new options in the empiric management of febrile granulocytopenic cancer patients. The possibility of administering monotherapy with certain third-generation cephalosporins (ceftazidime or cefoperazone) or the carbapenems (imipenem) is worthy of consideration. The licensure of each new agent has been accompanied by clinical trial data which, by many critera, are impressive. However, several factors must be borne in mind when evaluating these data. First, most investigative trials have exclusion criteria that eliminate the sickest patients from study such as those in shock, respiratory failure, and coma. Secondly, many potential candidates for investigative agents are realistically judged to be too ill for what, initially at least, may be a promising but unproved agent. Finally, method of analysis may confer an altered prospective of efficiency. The elimination of "unevaluable cases" removes patients who receive an insufficient course of therapy; analysis of those who survive a sufficient interval so they qualify for analysis produces a more favorable picture of clinical efficacy by definition. Finally, all of the studies to date assessing monotherapy have enrolled realtively small numbers of patients. With

these reservations in mind, Tables 29 to 31 summarize clinical and microbiologic data on several agents used in monotherapy of lower respiratory tract bacterial infections (136-144).

Table 30

Treatment of Nosocomial Pneumonia
with Ceftazidime

	Number of Patients		Favorable Clinical Response	
Study	P. aeruginosa	Overall	P. aeruginosa	Overall
Gozzard et al	6	7	6	7
Mandell et al	4	17	4	15
Francioli et al	9	11	8	9
Clumeck et al	4	11	3	9
Scully et al	2	5	1	4
Trenholme	13	18	12	16
Total	38	69	34 (90)	60 (88)

Gozzard, Lancet 1:1152, 1982
Mandell, J. Antimicrob. Chemother. 12:(Suppl A) 9, 1983
Francioli, J. Antimicrob. Chemother. 12:(Suppl A) 139, 1983
Clumeck, Antimicrob. Agents. Chemother. 24:176, 1983
Scully, Arch. Intern. Med. 144:57, 1984
Trenholme, Am. J. Med. 79:(Suppl 2A) 32, 1985

What, then, can be concluded about the role of monotherapy in febrile granulocytopenic cancer patients? The collective data suggests that monotherapy may well be safe and feasible. Clearly, the drug used for monotherapy is of critical importance. At this time ceftazidime, cefoperazone and imipenem appear to be the only agents that fulfill the critical requirements for studies in granulocytopenic patient populations. A critical factor which is at the present time unknown deals with the rate of emergence of resistant organisms in the context of monotherapy. However, should the current observations be confirmed and sustained, monotherapy may well find a role in the initial empiric treatment of hospital-acquired bacterial pneumonia in both nongranulocytopenic and granulocytopenic patients. This approach would clearly help to reduce the toxicity and cost associated with combination antibiotic administration, as well as reduce the inconvenience to the patients and the workloads of the medical, nursing and pharmacy staff. Certainly this prospect deserves further investigation. At the present time, however, I would feel more comfortable with a combined therapy regimen consisting of an aminoglycoside and a beta-lactam, particularly for neutropenic patients pending further comparative studies.

Table 31

Outcome of Patients Treated with Imipenem/Cilastatin for Pneumonia

	Bacteriologic Response/Episodes Satisfactory	Clinical Response/Episodes Satisfactory	Failure
	Number (Percent)		
Hospital Acquired (n = 29)	15 (52)	26 (90)	3 (10)
Community Acquired (n = 14)	11 (79)	14 (100)	0 (0)
Total Group (n = 43)	26 (60)	40 (93)	3 (7)

Salata, Am. J. Med. 78:Suppl 6A, 104, 1985

Other Respiratory Infections

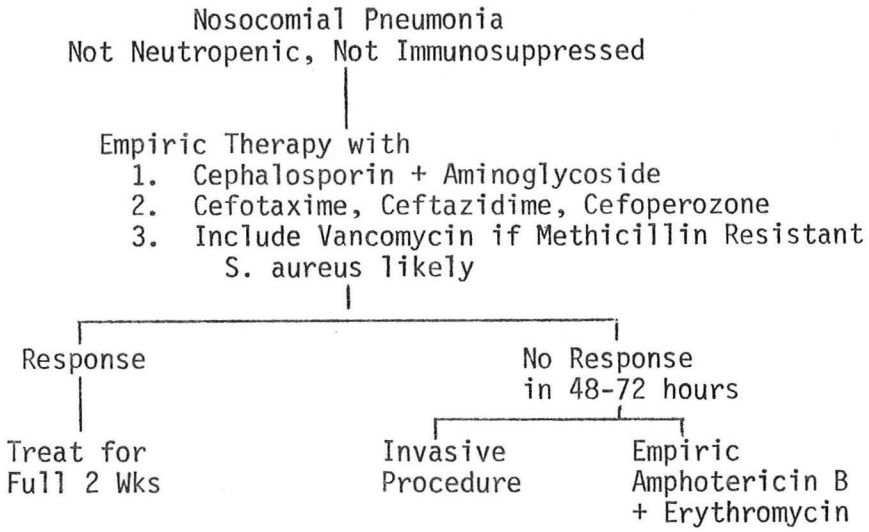
This review has concentrated on gram-negative infections of the lower respiratory tract which is an area of great concern for those involved in the management of nosocomial infections. There are other areas where modest progress has been made. For the treatment of *P. carinii* infection, trimethoprim-sulfamethoxazole has successfully been used in most immunosuppressed patients with histologically proven disease (145). The exception to this observation is pneumocystis infection in patients with acquired immune deficiency syndrome. In the area of viral infection, modest progress has been made with the development of vidarabine and acyclovir for herpes simplex and Varicella-zoster infections (146). Nonetheless, the effect of these two new antiviral agents, even in combination with interferon, against cytomegalovirus pneumonia has been extremely disappointing (147). Opportunistic fungal pneumonias are poorly treated with all available agents and usually do not respond unless there is amelioration of predisposing factors or improvement in underlying disease. The latter statement appears relevant to most patients with hospital-acquired pulmonary infections.

SUMMARY OF APPROACH

A summary of therapeutic approaches for three different categories of hospital-acquired pneumonias are shown in Tables 32-34. When bacterial infection cannot be excluded, as is usually the case, emperic broad-spectrum antibiotic coverage should be instituted within a few hours of the patient's presentation. Since Staphylococcus, Klebsiella and other more resistant gram-negative rods are most likely, a reasonable drug combination is a cephalosporin plus tobramycin.

Table 32

Clinical Approach to Management

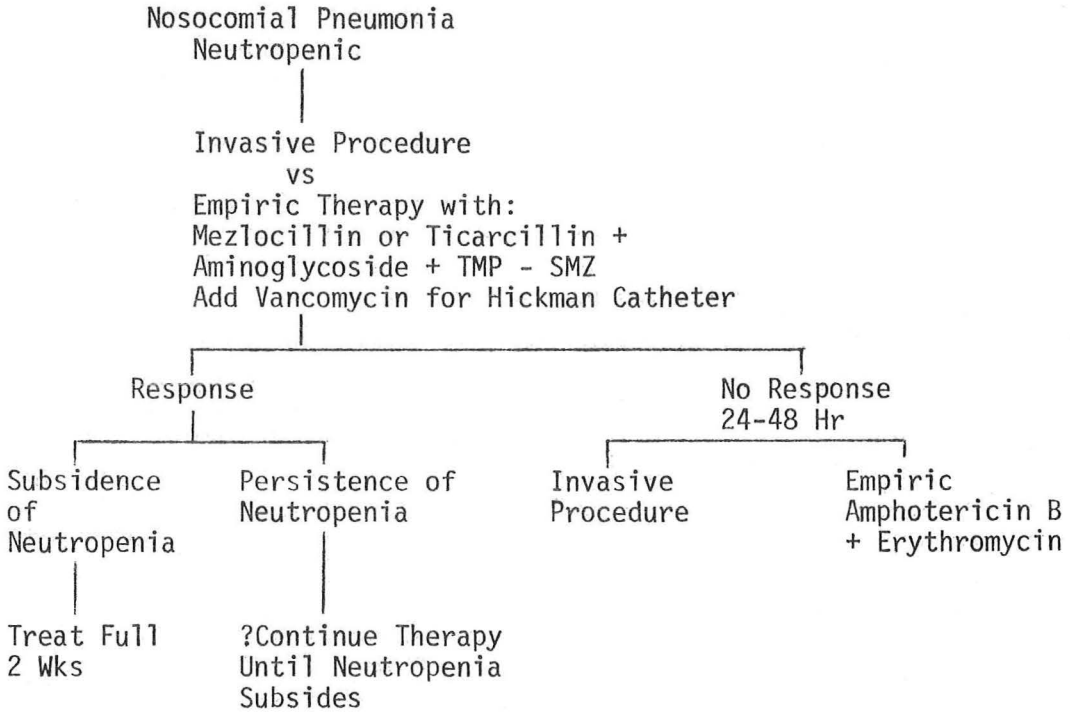


In the setting of patients with deficient cell mediated immunity, high dose trimethoprim-sulfamethoxazole should also be instituted as blind therapy for pneumocystis pneumonia. In patients who are neutropenic, a combination of mezlocillin or ticarcillin plus an aminoglycoside is probably most effective. For the most part, these patients are on trimethoprim-sulfamethoxazole prophylaxis, hence *Pneumocystis carinii* infection is generally not an issue. However, if the patient has not been on trimethoprim-sulfamethoxazole this should be added as well. Methicillin-resistant Staphylococci are a common problem in Parkland Hospital. Vancomycin should be added to this empiric therapy in circumstances where methicillin-resistant *S. aureus* is likely or in neutropenic patients with Hickman catheters in place. Alternatively, in patients who are not neutropenic and not immunosuppressed and who do not appear to be septic, a third-generation cephalosporins, such as cefotaxime, ceftazidime or cefoperazone might be utilized since they have shown results in preliminary studies which are comparable to antibiotic combinations. The effect of utilizing third-generation cephalosporins on bacterial resistance patterns is unknown. In patients who are either neutropenic or who have deficient cell-mediated immunity, an invasive procedure to provide a diagnosis should be considered rather than beginning empiric therapy. If empiric therapy is chosen, an invasive procedure should be performed if no clinical response is obtained in 48 to 72 hours with local infiltrates and sooner in the setting of diffuse bilateral disease or neutropenia. Fiberoptic bronchoscopy with washings, sterile brushings and transbronchial biopsy has been a useful procedure in certain circumstances. If procedures are carefully scheduled with both the pulmonary physician and the pathologist, bronchoscopic biopsy specimens can be fixed and stained within 3 to 4 hours using modern techniques, and thus, an open lung biopsy could be done the same day as bronchoscopy if the latter procedure does not

provide a diagnosis. Open lung biopsy would be preferable when the leading clinical diagnosis is a noninfectious cause such as drug-induced pneumonitis since small specimens obtained with transbronchial biopsy increase the chance of false-negative results in such cases. Open lung biopsy is also preferable in patients whose disease is progressing so rapidly that the risks of possible delay in tissue diagnosis mandate the performance of a single procedure. Percutaneous needle aspiration is useful as an initial procedure in patients with peripheral and localized disease. If the patient responds to therapy, therapy should be continued for a full two weeks or possibly until neutropenia subsides.

Table 33

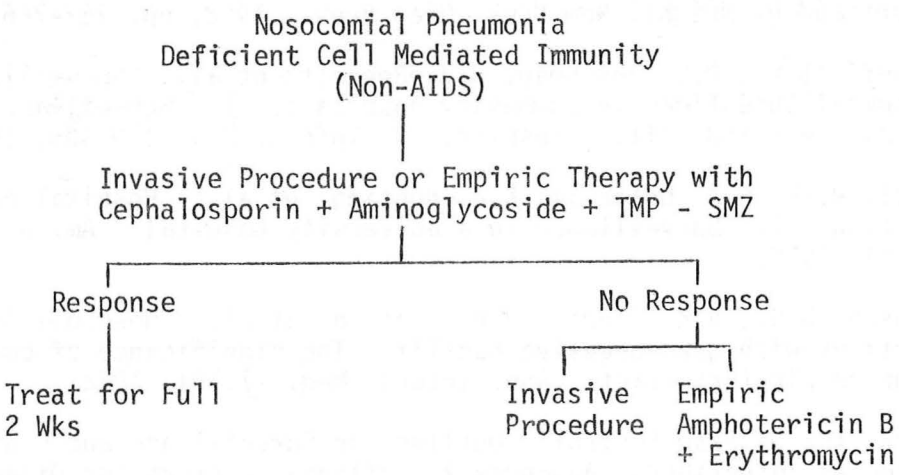
Clinical Approach to Management



The most difficult group of patients with which to deal are those with fever and infiltrates that persist in spite of the empiric use of broad spectrum antibiotics. In patients at risk for invasive fungal infections (focal infiltrates, leukopenia, antecedent broad-spectrum antibiotic coverage for a week or more and recent cytotoxic/adrenocorticosteroid therapy) empiric Amphotericin B should be stongly considered or an invasive procedure to make this diagnosis should be performed. In certain cases where a progressive consolidating pneumonia, combined with suggestive gastrointestinal or neurological symptomatology makes Legionnaire's disease a diagnostic possibility, erythromycin (1 gram intraveneously every 6 hours) may be incorporated into the antibiotic regimen.

Table 34

Clinical Approach to Management



With the advent of more specific and effective treatment, empiric therapy based on uncertain diagnostic impressions becomes increasingly undesirable. Further developments in noninvasive techniques for the diagnosis of pulmonary infection in the immunocompromised host may minimize the need for such an approach. Alternately, as newer antibiotics with ever increasing spectra of activity are utilized, monotherapy may be possible for many patients. It is likely that careful monitoring will still be required since it is unlikely that any drug or combination of drugs will provide complete and sustained coverage in all patients. There are, after all, never easy solutions to multi-factoral problems.

PNEUMONIA: LIEUTENANT OF THE MEN OF DEATH

A little over 75 years ago, Sir William Osler borrowed the phrase "Captain of the Men of Death" from John Bunyan and applied it to pneumonia, which he described as one of the most widespread and fatal of all acute diseases (148). He considered the pneumococcus to be the sole etiology of lobar pneumonia, but postulated that other organisms might contribute to this infection as secondary invaders (149). Osler also knew that the pneumococcus as well as the other bacteria were commonly found as part of the normal oral and pharyngeal flora, and that pneumonia probably resulted from colonization with a particularly virulent strain or from a breakdown in normal host defenses. Although antibiotics dramatically changed the mortality rate, pneumonia remains the seventh leading cause of premature death in the United States (150). In addition, as outlined in this review, pulmonary infections are common in patients with other serious illnesses and are frequently contributing factors to death in critical care units (14). There continues to be a need for research in this illness. If pneumonia is no longer a captain, it at least seems to deserve a commissioned rank. Perhaps "Lieutenant of the Men of Death" is appropriate.

REFERENCES

1. Norris, G.W.: Lobar pneumonia, in *Modern Medicine*, edited by W. Osler and T. McCrae, Philadelphia, Lea and Febiger, 1913, pp. 202-286.

2. Fleming, A.: Chemotherapy, in *Great Adventures in Medicine*, edited by S. Rapport and H. Wright, New York, Dial Press, 1952, pp. 757-766.

3. Eickhoff, T.C., P.S. Brachman, J.V. Bennett, et al.: Surveillance of nosocomial infections in community hospitals. I. Surveillance methods, effectiveness and initial results. J. Infect. Dis. 120:305, 1969.

4. Wenzel, R.P., C.A. Osterman, K.J. Hunting, et al.: Hospital acquired infection. I. Surveillance in a university hospital. Am. J. Epidem. 103:251, 1976.

5. Johanson, W.G., A.K. Pierce, J.P. Sanford, et al.: Nosocomial respiratory infections with gram-negative bacilli: The significance of colonization of the respiratory tract. Ann. Intern. Med. 77:701, 1972.

6. Centers for Disease Control: Outline for Surveillance and Control of Nosocomial Infections. Appendix 2. Atlanta, Centers for Disease Control, 1976.

7. Haley, R.W., D. Quade, H.E. Freeman, et al.: CDC-SENIC Planning Committee: Study on the efficacy of nosocomial infection control (SENIC Project): Summary of study design. Am. J. Epidemiol., 111:472, 1980.

8. Andrews, C.P., J.J. Coalson, J.D. Smith, et al.: Diagnosis of nosocomial bacterial pneumonia in acute, diffuse lung injury. Chest, 80:255, 1981.

9. Bennett, J.V., W.E. Scheckler, D.G. Maki, et al.: Current national patterns, in *Proceedings of the International Conference on Nosocomial Infections*, edited by P.S. Brachman and T.C. Eickhoff, Chicago, American Hospital Association, 1971, pp. 42-49.

10. Centers for Disease Control: National Nosocomial Infections Study Report, Annual Summary 1979, Atlanta, Centers for Disease Control, March 1982.

11. Haley, R.W., T.M. Hooton, D.H. Culver, et al.: Nosocomial infections in U.S. hospitals, 1975-1976. Am. J. Med. 70:947, 1981.

12. Haley, R.W., D.H. Culver, J.W. White, et al.: The nationwide nosocomial infection rate: A new need for vital statistics. Am. J. Epidemiol. 121:159, 1985.

13. Hughes, J.M., V. Munn, W. Jarvis, et al.: Mortality associated with nosocomial infections in the United States 1975-1981. Twenty-second Interscience Conference on Antimicrobial Agents and Chemotherapy, p. 189 (Abstract).

14. Gross, P.A., H.C. Neu, P. Aswapokee, et al.: Deaths from nosocomial infections: Experience in a university hospital and a community hospital. Am. J. Med. 68:219, 1980.

15. National Center for Health Statistics (Haupt, B.J.): Utilization of Short Stay Hospitals: Annual Summary. Vital and Health Statistics. Series 13, No. 64, DHHS Publ. No. (PHS) 82-1725. Public Health Service, Washington, D.C., Government Printing Office, March 1982.

16. Dixon, R.E.: Effect of infections on hospital care. Ann. Intern. Med. 89:749, 1978.

17. Hughes, J.M., D.H. Culver, J.W. White, et al.: Nosocomial infections surveillance, 1980-1982. Morb. Mortal. Weekly Resp. 32:155, 1983.

18. Sanford, J.P. and A.K. Pierce: Current infection problems-Respiratory, in *Proceedings of the International Conference on Nosocomial Infections*, edited by P.S. Brachman and T.C. Eickhoff, Chicago, American Hospital Association, 1971, pp. 77-81.

19. Adelman, B.A, A. Bentman, P. Rosenthal, et al.: Treatment of aspergillosis in leukemia. Ann. Intern. Med. 91:323, 1979.

20. Aisner, J., S.C. Schimpff and P.H. Wiernik: Treatment of invasive aspergillosis: Relation of early diagnosis and treatment to response. Ann. Intern. Med. 86:539, 1977.

21. Meyer, R.D., P. Rosen and D. Armstrong: Phycomycosis complicating leukemia and lymphoma. Ann. Intern. Med. 77:871, 1972.

22. Masur, H., P.P. Rosen and D. Armstrong: Pulmonary disease caused by *Candida* species. Am. J. Med. 63:914, 1977.

23. Kaplan, M.H., P. Rosen and D. Armstrong: Cryptococcosis in cancer hospital: Clinical and pathological correlates in forty-six patients. Cancer, 39:2265, 1977.

24. Fisher, B.D. and D. Armstrong: Cryptococcal interstitial pneumonia: Value of antigen determination.N. Engl. J. Med. 297:1440, 1977.

25. Goodwell, B., J.B. Jacobs, B.D. Powell, et al.: *Pneumocystis carinii:* The spectrum of diffuse interstitial pneumonia in patients with neoplastic diseases. Ann. Intern. Med. 72:337, 1970.

26. Hughes, W.T, S. Kuhn, S. Chandhary, et al.: Successful chemoprophylaxis for *Pneumocystis carinii* pneumonitis. N. Engl. J. Med. 297:1419, 1977.

27. Remington, J.S.: Toxoplasmosis in the adult. Bul. N.Y. Acad. Med. 50:211, 1974.

28. Ramsey, P.G., R.H. Rubin, N.E. Tolkoff-Rubin, et al.: The renal transplant patient with fever and pulmonary infiltrates: Etiology, clinical manifestations, and management. Medicine 59:206, 1980.

29. Rubin, R.H., P.S. Russell, M. Levin, et al.: Summary of a workshop on cytomegalovirus infections during organ transplantation. J. Infect. Dis. 139:728, 1979.

30. Meyers, J.D., H.C. Spencer, J.C. Watts, et al.: Cytomegalovirus pneumonia after human marrow transplantation. Ann. Intern. Med. 82:181, 1975.

31. Williams, D.M., J.A. Krick and J.S. Remington: Pulmonary interaction in the compromised host. Am. Rev. Respir. Dis. 114(Part 1):359 and 114(Part 2): 593, 1976.

32. Mathur, U, D.W. Bentley and C.B. Hall: Concurrent respiratory syncytial virus and influenza A infections in the institutionalized elderly and chronically ill. Ann. Intern. Med. 93:49, 1980.

33. DeFabritus, A.M., R.R. Riggio, D.S. David, et al.: Parainfluenza type 3 in a transplant unit. J.A.M.A. 241:384, 1979.

34. Kapila, R., D.E. Lintz, F.T. Tecson, et al.: A nosocomial outbreak of influenza A. Chest 71:576, 1977.

35. Centers for Disease Control: Influenza A in a hospital-Illinois. Morbid. Mortal. Weekly Rep. 30:79, 1981.

36. VanVoris, L.P., R.B. Belshe and J.L. Shaffer: Nosocomial influenza B virus infection in the elderly. Ann. Intern. Med. 96:153, 1982.

37. Young, L.S., D. Armstrong, B. Blevins, et al.: *Nocardia asteroides* infection complicating neoplastic disease. Am. J. Med. 50:356, 1979.

38. Krick, J.A., E.B. Stinson and J.S. Remington: Nocardia infection in heart transplant patients. Ann. Intern. Med. 82:18, 1975.

39. Ehrenkranz, H.N. and J.L. Klicklighter: Tuberculosis outbreak in a general hospital. Evidence of airborne spread of infection. Ann. Intern. Med. 77:377, 1972.

40. Feld, R., G.P. Bodey and D. Groschel: Mycobacterioses in pateints with malignant disease. Arch. Intern. Med. 136:67, 1976.

41. Yu, V.L., F.J. Krobroth, J. Shonnard, et al.: Legionnaires' disease: New clinical perspective from a prospective pneumonia study. Am. J. Med. 73:357, 1982.

42. Cohen, M.L., C.V. Broome, A.L. Paris, et al.: Fatal nosocomial Legionnaires' disease: Clinical and epidemiologic characteristics. Ann. Intern. Med. 90:611, 1979.

43. Fraser, D.W.: Bacteria newly recognized as nosocomial pathogens. Am. J. Med. 70:432, 1981.

44. Haley, C.E., M.L. Cohen, J. Halter, et al.: Nosocomial Legionnaire's disease: A continuing commonsource epidemic at Wadsworth Medical Center. Ann. Intern. Med. 90:583, 1979.

45. Kirby, B.D., K.M. Synder, R.D. Meyer, et al.: Legionnaires' disease: Report of sixty-five nosocomially acquired cases and review of the literature. Medicine 59:188, 1980.

46. Myerowitz, R.L., A.W. Pasculle, J.N. Dowling, et al.: Opportunistic lung infection due to Pittsburgh pneumonia agent. N. Engl. J. Med. 301:953, 1979.

47. Yu, V.L., J.J. Zuravlef, E.M. Elder, et al.: Pittsburgh pneumonia agent may be a common cause of nosocomial pneumonia: Seroepidemiologic evidence. Ann. Intern. Med. 97:724, 1982.

48. Beem, M.O. and E.M. Saxon: Respiratory-tract colonization and a distinctive pneumonia syndrome in infants infected with *Chlamydia trachomatis*. N. Engl. J. Med. 296:306, 1977.

49. Simon, H.B., F.S. Southwick, R.C. Moellering, et al.: *Hemophilus influenzae* in hospitalized adults: Current perspectives. Am. J. Med. 69:219, 1980.

50. Reinarz, JA, A.K. Pierce, B.B. Mays, et al.: The potential role of inhalation therapy equipment in nosocomial pulmonary infections. J. Clin. Invest. 44:831, 1965.

51. Pierce, A.K., E.B. Edmondson, G. McGee, et al.: An analysis of factors predisposing to gram-negative bacillary necrotizing pneumonia. Am. Rev. Respir. Dis. 94:309, 1966.

52. Pierce, A.K., J.P. Sanford, G.B. Thomas , et al.: Long-term evaluation of decontamination of inhalation therapy equipment and the occurrence of necrotizing pneumonia. N. Engl. J. Med. 282:528, 1970.

53. Greene VW., D. Vesley, R.G. Bond, et al.: Microbiological contamination of hospital air. I. Quantitative studies. Appl. Microbiol. 10:561, 1962.

54. Mackowiak, PA: The normal microbial flora. N. Engl. J. Med. 307:83, 1982.

55. Johanson, W.G., Jr., A.K. Pierce and J.P. Sanford: Changing pharyngeal bacterial flora of hospitalized patients. Emergence of gram-negative bacilli. N. Engl. J. Med. 281:1137, 1969.

56. Johanson, W.G., Jr., A.K. Pierce, J.P. Sanford, et al.: Nosocomial respiratory infections with gram-negative bacilli: The significance of colonization in the respiratory tract. Ann. Intern. Med. 77:701, 1972.

57. Johanson, W.G. Jr., J.H. Higuchi, T. Chaudhuri, et al.: Bacterial adherance to epithelial cells in bacillary colonization of the respiratory tract. Am. Rev. Respir. Dis. 121:55, 1980.

58. Woods, D.E., D.C. Strauss, W.G. Johanson Jr., et al.: Role of pili: Adherence of *Pseudomonas aeruginosa* to mammalian buccal epithelial cells. Infect. Immun. 29:1146, 1980.

59. Ofek, I., D. Mirelman and N. Sharon: Adherence of *Escherica coli* to human mucosal cells mediated by mannose receptors. Native 265:623, 1977.

60. Inbar, M. and L. Sach. Interaction of a carbohydrate-binding protein Conconavalin A with normal and transformed cells. Proc. Natl. Acad. Sci. (USA) 63:1418, 1969.

61. Gibbons, R.J. and J. van Houte: Bacterial adherence in oral microbial ecology. Ann. Rev. Microbiol. 29:19, 1975.

62. Zetter, B.F., T.E. Daniels, C. Quadra-White, et al.: LETS protein in normal and pathological human oral epithelium. J. Dent. Res. 58:484, 1979.

63. Woods, D.E., D.C. Strauss, W.G. Johanson, Jr., et al.: Role of salivary protease activity in adherence of gram-negative bacilli to mammalian buccal epithelial cells *in vivo*. J. Clin. Invest. 68:1435, 1981.

64. Higuchi, JH and WG Johanson, Jr.: The relationship between adherence of *Pseudomonas aeruginosa* to upper respiratory cells *in vitro* and susceptibility to colonization *in vivo*. J. Lab. Clin. Med. 95:698, 1980.

65. Amberson, J.B., Jr.: Aspiration bronchopneumonia. Int. Anesthesiol. Clin. 3:126, 1937.

66. Huxley, E.J., J. Viroslav, W.R. Gray, et al.: Pharyngeal aspiration in normal adults and patients with depressed consciousness. Am. J. Med. 64:564, 1978.

67. Green, G.M., and E.H. Kass: Factors influencing the clearance of bacteria by the lung. J. Clin. Invest. 43:769, 1964.

68. Green, G.M. and E.H. Kass: The role of the alveolar macrophage in the clearance of bacteria by the lung. J. Exp. Med. 119:167, 1964.

69. Laurenzi, G.A., L. Berman, M. First, et al.: A quantitative study of the deposition and clearance of bacteria in the murine lung. J. Clin. Invest. 43:759, 1964.

70. Pierce, A.K., R.C. Reynolds and G.D. Harris: Leukocytic response to inhaled bacteria. Am. Rev. Respir. Dis. 116:679, 1977.

71. Gross, G.N., S.R. Rehm and A.K. Pierce: The effect of complement depletion on lung clearance of bacteria. J. Clin. Invest. 63:373, 1978.

72. Rehm, S.R., G.N. Gross and A.K. Pierce: Early bacterial clearance from murine lungs. Species-dependent phagocyte response. J. Clin. Invest. 66:194, 1980.

73. Ansfield, M.J., D.E. Woods and W.G. Johanson, Jr.: Lung bacterial clearance in murine pneumococcal pneumonia. Infect. Immun. 17:195, 1977.

74. Berendt, R.F.: Relationship of method of administration to respiratory virulence of *Klebsiella pneumoniae* for mice and squirrel monkeys. Infect. Immun. 20:581, 1978.

75. Onofrio, J.M., G.B. Toews, M.F. Lipscomb, et al.: Granluocyte-alveolar macrophage interaction in the pulmonary clearance of *Staphylococcus aureus*. Am. Rev. Respir. Dis. 127:335, 1983.

76. Toews, G.B. and W.C. Vial. The role of C5 in polymorphonuclear leukocyte recruitment in response to *Streptococcus pneumoniae*. Am. Rev. Respir. Dis. 129:82, 1984.

77. Larsen, G.L., B.C. Mitcher, T.B. Harper, et al.: The pulmonary response of C5 sufficient and deficient mice to *Pseudomonas aeruginosa*. Am. Rev. Respir. Dis. 126:306, 1982.

78. Merrill, W.W., G.P. Naegel, R.A. Matthay, et al.: Alveolar macrophage-derived chemotactic factor: Kinetics of *in vitro* production and partial characterization. J. Clin. Invest. 65:268, 1980.

79. Hunninghake, G.W., J.E. Gadek, H.M. Fales, et al.: Human alveolar macrophage-derived chemotactic factor for neutrophils. J. Clin. Invest. 66:473, 1980.

80. Hunninghake, G.W., J.I. Gallim and A.S. Fauci. Immunologic reactivity of the lung: The *in vivo* and *in vitro* generation of a neutrophil chemotactic factor by alveolar macrophages. Am. Rev. Respir. Dis. 117:15, 1978.

81. Pennington, J.E. and E.A. Harris: Influence of immunosuppression on alveolar macrophage chemotactic activities in guinea pigs. Am. Rev. Respir. Dis. 123:299, 1981.

82. Pennington, J.E., W.J. Matthews, J.T. Marino, et al.: Cyclophosphamide and cortisone acetate inhibit complement biosynthesis by guinea pig bronchoalveolar macrophages. J. Immunol. 123:1318, 1979.

83. Fels, A.O.S., N.A. Pawlowski, E.B. Cramer, et al.: Human alveolar macrophages produce leukotriene B_4. Proc. Natl. Acad. Sci. USA 79:7866, 1982.

84. Goetzl, E.J. and W.C. Pickett: The human PMN leukocyte chemotactic activity of complex hydroxyeicosatetraenoic acids (HETEs). J. Immunol. 125:1789, 1980.

85. Reynolds, H.Y.: Normal and defective respiratory host defenses, in *Respiratory Infections: Diagnosis and Management*, edited by J.E. Pennington, New York, Raven Press, 1983, pp. 1-23.

86. Polmar, S.H.: Immunodeficiency and pulmonary disease, in *Immunologic and Infectious Reactions in the Lung*, edited by C.H. Kirkpatrick and H.Y. Reynolds, New York, Marcel Dekker, 1976, pp. 191-201.

87. Oxelius, V.A., A.B. Laurell, B. Lindquist, et al.: IgG subclasses in selective IgA deficiency: Importance of IgG_2-IgA deficiency. N. Engl. J. Med. 304:1476, 1981.

88. Oxelius, V.A.: IgG subclass levels in infancy and childhood. Acta Paediatr. Scand. 68:23, 1979

89. Beck, C.S and D.C. Heiner: Selective immunoglobulin G_4 deficiency and recurrent infections of the respiratory tract. Am. Rev. Respir. Dis. 124:94, 1981.

90. LaForce, F.M., W.J. Kelly and G.L. Huber: Inactivation of staphylococci by alveolar macrophages with preliminary observations of the importance of alveolar lining material. Am. Rev. Respir. Dis. 108:784, 1973.

91. Coonrod, J.D. and K. Yoneda: Detection and partial characterization of antibacterial factor(s) in alveolar lung material of rats. J. Clin. Invest. 71:129, 1983.

92. Coonrod, J.D., R.L. Lester and L.C. Hsu: Characterization of the extracellular bactericidal factors of rat alveolar lining material. J. Clin. Invest. 74:1269, 1984.

93. Stamm, W.E.: Infections related to medical devices. Ann. Intern. Med. 89:764, 1978.

94. Weinstein, R.A., C. Nathan, R. Gruensfelder, et al.: Endemic aminoglycoside resistance in gram-negative bacilli: Epidemiology and mechanisms. J. Infect. Dis., 141:338, 1980.

95. Weinstein, R.A. and S.A. Kabins: Strategies for prevention and control of multiple drug-resistant nosocomial infection. Am. J. Med. 70:449, 1981.

96. Hooten, T.M., R.W. Haley, D.H. Culver, et al.: The joint associations of multiple risk factors with the occurrence of nosocomial infection. Am. J. Med. 70:960, 1981.

97. Bell, R., J.J. Coalson, J.D. Smith, et al.: Multiple organ system failure and infection in Adult Respiratory Distress Syndrome. Ann. Intern. Med. 99:293, 1983.

98. Rubin, R.H.: Infection in the renal transplant patient, in *Clinical Approach to Infection in the Compromised Host*, edited by R.H. Rubin and L.S. Young, New York, Plenum Medical Book Company, 1981, pp. 553-605.

99. Neiman, P.E., E.D. Thomas, W.C. Reeves, et al.: Opportunistic infection and intersititial pneumonia following marrow transplantation for aplastic anemia and hematologic malignancy. Transplant. Proc. 8:663, 1976.

100. Weiss, R.B. and F.M. Muggia: Cytotoxic drug-induced pulmonary disease: Update 1980. Amer. J. Med. 68:259, 1980.

101. Murray, P.R. and J.A. Washington, II: Microscopic and bacteriologic analysis of expectorated sputum. Mayo Clin. Proc. 50:339, 1975.

102. Zuravleff, JJ., V.L. Yu, J.W. Shonnard, et al.: Diagnosis of Legionnaires' disease: An update of laboratory methods with new emphasis on isolation by culture. J.A.M.A. 250:1981, 1983.

103. Singer, C., D. Armstrong, P. Rosen, et al.: Diffuse pulmonary infiltrates in immunosuppressed patients: Prospective study of 80 cases. Amer. J. Med. 66:110, 1979.

104. Davidson, M., B. Tempest and D.L. Palmer: Bacteriologic diagnosis of acute pneumonia: Comparison of sputum, transtracheal aspirates, and lung aspirates. J.A.M.A. 235:158, 1976.

105. Kalinske, R.W, R.H. Parker, D. Brandt, et al.: Diagnostic usefulness and safety of transtracheal aspiration. N. Engl. J. Med. 276:604, 1967.

106. Greenman, R.L. P.T. Goodal and D. King: Lung biopsy in immunocompromised hosts. Am. J. Med. 59:488, 1975.

107. Castellino, R.A. and N. Blank: Etiologic diagnosis of focal pulmonary infection in immunocompromised patients by fluoroscopically guided percutaneous needle aspiration. Radiology 132:563, 1979.

108. Bandt, P.D., N. Blank and R.A. Castellino: Needle diagnosis of pneumonitis: Value in high-risk patients. J.A.M.A. 220:1578, 1972.

109. Zavala, D.C. and J.E. Schoell: Ultrathin needle aspiration of the lung in infectious and malignant disease. Am. Rev. Respir. Dis. 123:125, 1981.

110. Feldman, N.T, J.E. Pennington and M.G. Ehrie: Transbronchial lung biopsy in the compromised host. J.A.M.A. 238:1377, 1977.

111. Cunningham, J.H., D.C. Zavala, R.J. Corry, et al.: Trephine air drill, bronchial brush and fiberoptic transbronchial lung biopsies in immunosuppressed patients. Am. Rev. Respr. Dis. 115:213, 1977.

112. Nishio, J.N. and J.P. Lynch, III: Fiberoptic bronchoscopy in the immunocompromised host: The significance of a "nonspecific" transbronchial bipsy. Am. Rev. Respir. Dis. 121:307, 1980.

113. Matthay, R.A., W.C. Farmer and D. Odero: Diagnostic fiberoptic bronchoscopy in the immunocompromised host with pulmonary infiltrates. Thorax 32:539, 1977.

114. Lauver, G.L., F.M. Haasan, R.B. Morgan, et al.: The usefulness of fiberoptic bronchoscopy in evaluating new pulmonary lesions in the immunocompromised host. Am. J. Med. 66:580, 1979.

115. Poe, R.H., M.J. Utel, R.H. Israel, et al.: Sensitivity and specificity of the non-specific transbronchial lung biopsy. Am. Rev. Respir. Dis. 119: 25, 1979.

116. Wimberly, N.W., J.B. Bass and B.W. Boyd: Use of a bronchoscopic protective catheter brush for the diagnosis of pulmonary infection. Chest 81:556, 1982

117. Wimberly, N.W., J. Faling and J.G. Bartlett: A fiberoptic bronchoscopy technique to obtain uncontaminated lower airway secretions for bacterial culture. Am. Rev. Respir. Dis. 119:337, 1979.

118. Higuchi, J.H., J.J. Coalson and W.G. Johanson, Jr.: Bacteriologic diagnosis of nosocomial pneumonia in primates. Am. Rev. Respir. Dis. 125:53, 1982.

119. Hayes, D.A., L.C. McCarthy and M. Friedman: Evaluation of two bronchofiberoptic methods of culturing the lower respiratory tract. Am. Rev. Respir. Dis. 122:319, 1980.

120. Broaddus, C., M.D. Dake, M.S. Stulbarg, et al.: Bronchoalveolar lavage and transbronchial biopsy for the diagnosis of pulmonary infections in the acquired immunodeficiency syndrome. Ann. Intern. Med. 102:747, 1985.

121. Stover, D.E., M.B. Zaman, S.I. Hajdu, et al.: Bronchoalveolar lavage in the diagnosis of diffuse pulmonary infiltrates in the immunosuppressed host. Ann. Intern. Med. 101:1, 1984.

122. Holle, R., R.C. Springmeyer, G. Hackman, et al.: Bronchoalveolar lavage diagnosis of viral pneumonia. Am. Rev. Respir. Dis. 127:194, 1983 (Abstract)

123. Rossiter, S.J. D.C. Miller, A.M. Churg, et al.: Open lung biopsy in the immunosuppressed patient: Is it really beneficial? J. Thorac. Cardiovasc. Surg. 77:338, 1979.

124. Wolfe, LJ, M.S. Bartlett, R.L. Baehner, et al.: The causes of interstitial pneumonitis in immunocompromised children: an aggressive systematic approach to diagnosis. Pediatrics 60:41, 1977.

125. Leight, G.S, Jr. and L.L. Michaelis: Open lung biopsy for the diagnosis of acute, diffuse pulmonary infiltrates in the immunosuppressed patient. Chest 73:477, 1978.

126. Rosen, P.P., N. Martini and D. Armstrong: *Pneumocystis carinii* pneumonia: Diagnosis by lung biopsy. Amer. J. Med. 58:794, 1975.

127. Pennington, J.E. and N.T. Feldman: Pulmonary infiltrates and fever in patients with hematologic malignancy. Assessment of transbronchial biopsy. Am. J. Med. 62:581, 1977.

128. Pennington, J.E.: Successful treatment of aspergillus pneumonia in hematologic neoplasia. N. Engl. J. Med. 295:426, 1976.

129. Pennington, J.E.: Aspergillus pneumonia in hematologic malignancy: Improvements in diagnosis and therapy. Arch. Intern. Med. 137:769, 1977.

130. Waldvogel, F.A.: Antibiotic treatment of gram-negative bacillary pneumonia, in *Aerobic Gram-Negative Bronchopneumonias*, edited by J.S. Thys, J. Klastersky and E. Yourassowsky. Oxford, Pergamon Press, 1980, pp. 109-125.

131. Klastersky, J.: Empiric treatment of infections in neutropenic patients with cancer. Rev. Infect. Dis. 5(Suppl):S21, 1983.

132. Pennington, J.E.: Penetration of antibiotics into respiratory secretions. Rev. Infect. Dis. 3:67, 1981.

133. Smith, B.R. and J.L. LeFrock: Bronchial tree penetration of antibiotics. Chest 83:904, 1983.

134. Maxwell, D.: The role of antibiotics given by inhalation in chronic chest disease. J. Antimicrob. Chemother. 11:203, 1983.

135. Young, L.S. and W.L. Hewitt: Activity of five aminoglycoside antibiotics *in vitro* against gram-negative bacilli and *Staphylococcus aureus*. Anitimicrob. Agents Chemother. 4:617, 1973.

136. Perkins, R.L.: Clinical trials of cefotaxime for the treatment of bacterial infections of the lower respiratory tract. Rev. Infect. Dis. 4(Suppl):S421, 1982.

137. Gardner, W.G.: Multicentered clinical evaluation of cefoperazone for the treatment of lower respiratory trace infections. Rev. Infect. Dis. 5(Suppl):S137, 1983.

138. Gozzard, D.I, A.M. Geddes, I.D. Farrell, et al.: Ceftazidime-a new extended-spectrum cephalosporin. Lancet 1:1152, 1982.

139. Mandell, L.A., L.E. Nicolle, A.R. Ronad, et al.: A multicentre prospective randomized trial comparing ceftazidme with cefazolin/tobramycin in the treatment of hospitalized patients with non-pneumococcal pneumonia. J. Antimicrob. Chemoter. 12(Suppl A):9, 1983.

140. Francioli, P, M. Clement, S. Geroulanos, et al.: Ceftazidime in severe infections: A Swiss multicentre study. J. Antimicrob. Chemother. 12(Suppl A): 139, 1983.

141. Clumeck, N, Y.V. Laethem, B. Bordt, et al.: Use of ceftazidime in the therapy of serious infections, including those due to multiresistant organisms. Anitmicrob. Agents Chemother. 24:176, 1983.

142. Scully, B.E. and H.C. Neu: Clinical efficacy of ceftazidime: Treatment of serious infection due to multiresistant Pseudomonas and other gram-negative bacteria. Arch. Intern. Med. 144:57, 1984.

143. Trenholme, G.M., J.C. Pollage and P.H. Karakusis: Use of Ceftazadime in the treatment of nosocomial lower respiratory tract infections. Am. J. Med. 79(Suppl 2A):32, 1985.

144. Salata, R.A., R.L. Gebhart, D.L. Palmer, et al.: Pneumonia treated with Imipenem/Cilastatin. Am. J. Med. 78(Suppl 6A):104, 1985.

145. Young, L.S.: Trimethoprim-sulfamethoxazole in the treatment of adults with pneumonia due to *Pneumocystis carinii*. Rev. Infect. Dis. 4:608, 1982.

146. Young, L.S.: Host defenses against viral infection and the outlook for antiviral therapy. Schweiz Med. Wschr. 1113(Suppl 14):20, 1983.

147. Wade, J.C. and J.D. Meyers: Treatment of cytomegalovirus pneumonia after marrow transplantation. J. Cell Biochem. 7A(Suppl):65, 1983.

148. Osler, W: The principles and practice of medicine, Edition 4, New York, D. Appleton and Co., 1901, p. 108.

149. Osler, W: The principles and practice of medicine, Edition 7, New York, D. Appleton and Co., 1901, p. 108.

150. Mortality and Morbidity Weekly Report 31:111, 1983.