

# American Thoracic Society

MEDICAL SECTION OF THE AMERICAN LUNG ASSOCIATION

## Hospital-acquired Pneumonia in Adults: Diagnosis, Assessment of Severity, Initial Antimicrobial Therapy, and Preventative Strategies

### A Consensus Statement

THIS OFFICIAL STATEMENT OF THE AMERICAN THORACIC SOCIETY WAS ADOPTED BY THE ATS BOARD OF DIRECTORS, NOVEMBER 1995.

Hospital-acquired pneumonia (HAP) remains an important cause of mortality and morbidity despite the introduction of potent broad-spectrum antimicrobial agents, complex supportive care modalities, and the use of preventive measures. HAP, defined as pneumonia occurring  $\geq 48$  h after admission and excluding any infection that is incubating at the time of admission, is not a reportable illness (1, 2). However, available data suggest that it occurs at a rate of between 5 to 10 cases per 1,000 hospital admissions, with the incidence increasing by as much as six- to 20-fold in patients who are being ventilated mechanically (1, 3-5). Pneumonia is currently the second most common nosocomial infection in the United States but has the highest mortality and morbidity (1, 3, 6, 6a, 7), and its presence increases hospital stay by an average of 7-9 d per patient.

Although the crude mortality rate for patients with HAP may be as high as 70%, all of these deaths are not the direct result of infection. The mortality attributable to pneumonia, or the "attributable mortality," has been defined as the percentage of HAP deaths that would not have occurred in the absence of this infection (7-9). Studies have estimated that between one third to one half of all HAP deaths are the direct result of infection, but the attributable mortality may be higher if bacteremia is present or if the etiologic agent is *Pseudomonas aeruginosa* or *Acinetobacter* species (8, 10).

The past decade has brought numerous changes in the clinical approach to HAP, and there has been an increased understanding of the pathogenesis, diagnosis, therapy, and prevention of this illness. This document is a summary of a consensus conference that was convened to review the available information and to develop a practical approach to the initial management of HAP. Participants included specialists in pulmonary and critical care medicine, infectious diseases, and surgical critical care. The current literature was evaluated, and in defining the microbiology of HAP, the panel focused on prospective studies that used careful, well-defined microbiologic methods and techniques. It is important to note that we often reached conclusions about the bacteriology of HAP from investigations that placed a particular emphasis on quantitative microbiologic methods, even though many of these studies were done in only a few centers in the United States and western Europe and their widespread applicability is unestablished. Therapeutic recommendations were developed whenever possible from data published in peer-reviewed papers, including randomized controlled trials, reviews, and case series. In some instances, a consensus of clinical experience of the participants formed the basis for decisions. Consensus was achieved by discussion among the participants, with deference to the majority opinion in cases of disagreement.

This statement was written with an awareness of ongoing areas of incomplete knowledge. The problems and controversies sur-

rounding the diagnosis of HAP have been reviewed recently (11, 12), and, rather than try to resolve these issues, the committee agreed to develop an approach to therapy that could be used for the initial management of suspected HAP, after the individual physician's own criteria for initiating therapy had been met (see discussion regarding different methods of diagnosing HAP). In addition, although broad categories of patient types and microbiologic patterns are presented, we recognize that a consideration of local bacterial spectra and the presence of antimicrobial resistance also are essential in formulating initial empiric therapy. Antibiotic resistance strains are an increasing problem; therefore, careful knowledge of local patterns of antimicrobial susceptibility should be incorporated into any empiric treatment regimen. Finally, this statement presents therapeutic algorithms that are based on the expected antimicrobial spectrum of commonly used antibiotics, and there are only a limited number of prospective randomized controlled trials that document the efficacy or superiority of specific regimens. In spite of these limitations, HAP remains a common and serious problem, and the committee agreed that development of a logical management approach, using all available data, would be useful to physicians who manage these patients.

The approach presented here relies on assessments of disease severity, the presence of risk factors for specific organisms, and time of onset of HAP to guide initial antibiotic selection. This document is an expansion of a previously published Canadian statement on the initial management of HAP (2) and is written to be a companion document to the ATS statement on community-acquired pneumonia (13). In addition to presenting an approach to initial therapy, the document explains how to recognize and evaluate the patient who is not responding to initial empiric therapy. Although no clearly effective, widely applicable preventive strategy for HAP exists, a number of novel approaches have been developed, and these were also examined.

The optimal management of patients with HAP requires close collaboration among pulmonary and critical care specialists, infectious disease practitioners, infection control practitioners, and hospital microbiologists. This type of collaboration will lead to early recognition and appropriate management of common source outbreaks and multiply-resistant pathogens. These recommendations are not intended to be applied to patients with recognized immunosuppression as a result of AIDS, hematologic malignancy, neutropenia, or transplantation. However, the presence of immunocompromised condition, particularly HIV infection, may not be known; thus, the potential presence of immune suppression should always be considered.

#### PATHOCENESIS OF HOSPITAL-ACQUIRED PNEUMONIA

For respiratory infection to occur, at least one of three conditions must be present: host defenses must be impaired, an in-

oculum of organisms of sufficient number must reach the patient's lower respiratory tract and overwhelm the host's defenses, or a highly virulent organism must be present.

#### Routes of Bacterial Entry

Entry into the lungs may occur by various routes, including microaspiration of oropharyngeal secretions colonized with pathogenic bacteria, aspiration of esophageal/gastric contents, inhalation of an infected aerosol, hematogenous spread from a distant site of infection, exogenous penetration from an infected site (in, pleural space), direct inoculation into the airways of intubated patients from ICU personnel or, questionably, translocation from the gastrointestinal tract.

Not all routes are equally effective means of entry for any given pathogen. Of the potential routes of entry into the lower respiratory tract, microaspiration of a small volume of oropharyngeal secretions previously colonized with pathogenic bacteria is the most common (1, 3, 14). While microaspiration is a frequent event, reported to occur in as many as 45% of healthy volunteers during sleep (15), it is the presence of pathogenic bacteria that are able to overwhelm the lower respiratory tract defenses that is important in the development of pneumonia. In one study, oropharyngeal colonization by enteric gram-negative bacilli (EGNB) was relatively rare (< 10%) or of short duration among healthy, nonhospitalized individuals, but as patients developed more severe systemic illness, the incidence of oropharyngeal colonization by EGNB increased to 35% in moderately ill patients and to 75% among critically ill patients (16). Not surprisingly, upper airway colonization and pneumonia frequently coexist (14, 16).

Gross aspiration of large volumes of material as a cause of HAP is less common, but when it occurs it can include both oropharyngeal and esophageal/gastric contents. The incidence of aspiration increases when the gag reflex is impaired, if there is an alteration in the patient's level of consciousness, when certain devices such as nasogastric or endotracheal tubes are used, or if esophageal disease is present (1, 15). The aerosol route is an effective method for the spread of *Legionella* spp., certain viruses, *Mycobacterium tuberculosis*, and fungi, as well as in the setting of a contaminated humidification reservoir during mechanical ventilation (17). Hematogenous spread from distant sites of infection is especially noted in the postoperative patient and in patients with chronic intravenous or genito-urinary catheters in place.

Among mechanically ventilated patients, additional routes of entry exist. The endotracheal tube bypasses host defenses above the vocal cords and impairs lower respiratory tract defenses such as cough and mucociliary clearance. Contaminated secretions can pool above the inflated endotracheal tube cuff and are not easily removed by suctioning. These secretions can leak around the endotracheal tube cuff and directly enter the lower respiratory tract when there are changes in airway caliber during swallowing and breathing. In addition, if medical staff or respiratory therapy equipment harbor pathogenic flora, bacteria can be directly inoculated into the tracheobronchial tree. For example, *Pseudomonas* species are known to colonize the tracheobronchial tree without first appearing in the oropharyngeal secretions of intubated patients, presumably entering the lung via direct inoculation (18). These factors increase the incidence of HAP in mechanically ventilated individuals and can account for differences in the spectrum of potential pathogens (especially the prominence of *P. aeruginosa* and *Acinetobacter* spp.) in this population when compared with other patients who develop HAP.

#### How Specific Risk Factors Lead to Pneumonia

The risk factors for respiratory tract colonization and HAP have considerable overlap and include patient-related conditions, in-

fection control-related problems, and intervention-related alterations in host defenses or bacterial exposure.

**Patient-related risk factors.** Certain illnesses predispose to colonization and pneumonia because of disease-associated impairments in host defensive function. These include severe acute or chronic illness, coma, malnutrition, prolonged hospitalization and/or preoperative period, hypotension, metabolic acidosis, cigarette smoking, and the presence of a number of comorbid illnesses. These illnesses include central nervous system (CNS) dysfunction, chronic obstructive lung disease (COPD), diabetes mellitus, alcoholism, azotemia, and respiratory failure (1, 3-5, 19). Advanced age is associated with an increased risk of pneumonia primarily because of the increased frequency of serious comorbidity among the elderly, but age-associated immune changes also play a role (20).

**Infection control-related factors.** Hospitalized patients commonly are exposed to potentially large inocula of bacteria from a number of sources. Poor infection control practices can lead to the transmission of hospital-acquired pathogens by the hands of medical personnel. This can occur either by not washing hands or not changing gloves between patients, or through the use of contaminated respiratory therapy devices and equipment (21, 22). Respiratory therapy devices can deliver large numbers of bacteria to the lung if contaminated condensate in the mechanical ventilator tubing washes back to the patient. The gastrointestinal tract also may be a source of large quantities of EGNB that can enter the tracheobronchial tree. Although investigators disagree whether gastric overgrowth leads to respiratory tract colonization and pneumonia, colonization at one of the two sites often predicts nearly simultaneous colonization at the other site (1, 3, 5, 23, 24).

**Intervention-related factors.** A number of procedures and therapies can lead to both host defense impairment and increased exposure to large inocula of bacteria (1, 5, 21-25). Certain therapeutic agents, particularly sedatives, can suppress CNS function and lead to an increased incidence of aspiration. Corticosteroids and cytotoxic agents impair a number of vital host defensive functions. Prolonged or complicated surgery, especially thoraco-abdominal procedures, is associated with a number of changes in mucociliary function and cellular host defenses that lead to increased rates of oropharyngeal colonization and pneumonia. Similarly, endotracheal tubes can impair mucociliary and mechanical clearance from the lower airways, as well as injure the epithelial surface and predispose to increased bacterial binding to the surface of the lower respiratory tract.

Many therapeutic interventions increase the exposure of hospitalized patients to large bacterial inocula. For example, prolonged and inappropriate use of antibiotics may increase colonization by antibiotic-resistant bacteria, including potentially virulent gram-negative bacilli (22). Antacids and histamine type 2 (H-2) blockers are commonly used for prophylaxis against stress gastritis and ulceration but may increase the frequency of gastric colonization by EGNB, and possibly the incidence of pneumonia (1, 5, 23, 24). Also, enteral feedings via a nasogastric tube can result in increased gastric volume, reflux, and gram-negative bacterial overgrowth in the stomach (26). Nasogastric tubes themselves probably impair the function of the lower esophageal sphincter, thereby promoting aspiration and bacterial contamination of the tracheobronchial tree. The effect of all these manipulations is augmented if patients are maintained in the supine position, because this position increases the rate of reflux of gastric contents into the lung (25). The endotracheal tube not only interferes with host defenses but also can become encrusted with a bacterial biofilm that may embolize to the lung (27). Also, contaminated secretions can pool above the inflated endotracheal tube cuff and may leak around the endotracheal cuff, directly entering the lower respiratory tract.

## MICROBIOLOGY OF HOSPITAL-ACQUIRED PNEUMONIA

The spectrum of potential pathogens associated with HAP differs from that of community-acquired pneumonia. Because microaspiration of upper airway secretions, heavily colonized with pathogenic bacteria, is by far the most common route of pathogen entry into the lower respiratory tract, the etiology of HAP depends largely on the type of organisms colonizing the oropharynx. The role of viruses in HAP has yet to be clarified because their presence is not commonly sought in the workup of HAP. It is known that viral HAP does occur and the sources of infection may be within the hospital as well as from the community. Viral pathogens should be considered at the time of epidemic nosocomial infection, particularly if there is a documented community outbreak of viral illness (17).

The bacterial pathogens that are most frequently associated with HAP are EGNB and *Staphylococcus aureus* (1, 28–34), but accumulating data suggest that in up to half of mechanically ventilated patients, the etiology of HAP is polymicrobial (1, 28, 33). When studies have evaluated risk factors for infection by specific organisms, the diagnosis of pneumonia is usually established on clinical grounds, but the bacteriology is defined by cultures of samples collected by protected specimen brushing (PSB) and/or bronchoalveolar lavage (BAL), blood cultures, expectorated sputum, or endotracheal suctioning.

The spectrum of potential pathogens can be defined by assessment of a variety of factors, including the severity of the pneumonia itself, the presence of specific co-existing illness, prior therapy (including antibiotics), and length of hospitalization. Recognition of these factors allows separation of patient populations into easily identifiable groups that form the basis for therapeutic decisions regarding treatment regimens. To classify a patient appropriately, three questions must be addressed: (1) Is the pneumonic illness mild to moderate or is it severe? (2) Are specific host or therapeutic factors, predisposing to specific pathogens, present? (3) Is the pneumonia early onset (occurring within < 5 d of admission) or late onset (occurring  $\geq$  5 d of admission) (30, 34)?

As shown in the Figure, once these determinations are made patients fall into one of three groups, each with its own likely set of pathogens. These groups are: (1) patients without unusual risk factors who present with mild-to-moderate HAP with onset at any time during hospitalization or severe HAP of early onset (Table 1); (2) patients with specific risk factors who present with mild-to-moderate HAP occurring any time during hospitalization (Table 2); and (3) patients with severe HAP either of early onset with specific risk factors or of late onset (Table 3).

Patients without risk factors who present with mild-to-moderate HAP occurring any time during hospitalization or severe HAP of early onset are likely to be infected with a specific group of "core organisms" (Table 1). These organisms also should be considered for all other patients, (thus, the term "core organisms") but patients who are described in Tables 2 and 3 are at risk for additional pathogens as well. The core organisms include: EGNB, such as *Enterobacter* spp., *Escherichia coli*, *Klebsiella* spp., *Proteus* spp., and *Serratia marcescens*, *Hemophilus influenzae*; and gram-positive organisms, such as methicillin-sensitive *S. aureus* and *Streptococcus pneumoniae*. Not included among the core organisms are highly resistant gram-negative organisms, such as *P. aeruginosa*, and *Acinetobacter* spp., and methicillin-resistant *S. aureus* (MRSA).

### Mild-to-Moderate HAP

In patients presenting with mild-to-moderate HAP, the spectrum of pathogens is influenced primarily by the presence or absence of risk factors for specific pathogens. In addition, the length of hospital stay before the occurrence of HAP influences the fre-

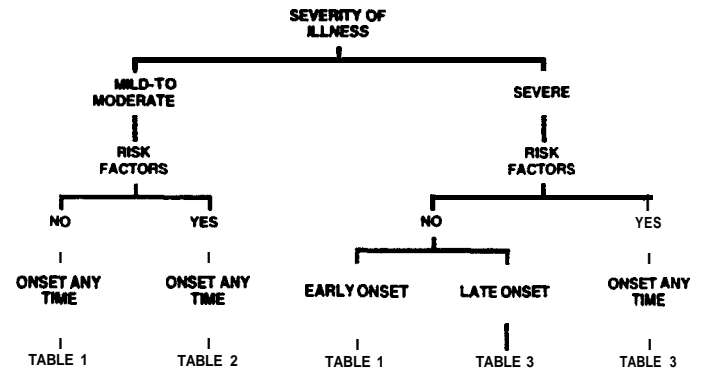


Figure 1. Algorithm for classifying patients with hospital-acquired pneumonia (HAP).

quency of recovering certain bacteria among the core organisms. For example, if HAP occurs within < 5 d of hospitalization, *H. influenzae*, *S. pneumoniae*, and *S. aureus* are more frequently isolated than other core pathogens (Table 1) (30, 34, 44). In one study of patients with mild-to-moderate HAP in a community hospital, the most common pathogens were *S. pneumoniae* and *H. influenzae*, which accounted for 31% of all cases (30). Gram-negative bacilli were found in 24% of episodes, and *S. aureus* in up to 10% of all episodes. In the remaining patients, either no pathogen was isolated or the pneumonia was polymicrobial.

In patients with mild-to-moderate HAP, the likely pathogens can be altered by the presence of specific risk factors (Table 2). In this setting, the frequently encountered pathogens include not only the core organisms but also other bacteria, depending on which risk factor is present. Specific comorbidities or therapies that predispose to pneumonia with certain pathogens are detailed in Table 2. For example, if a patient has a witnessed episode of aspiration, anaerobic bacteria, as well as the core organisms (especially gram-negative bacilli), should be considered, although the incidence of anaerobic HAP, even in this setting, is uncertain (35). However, if the patient has poor dentition or has aspirated acidified gastric contents (pH < 3.5), gram-negative bacteria are less likely to be a cause of HAP (23, 24, 36). In many hospitalized patients, aspirated gastric contents are not acidic (as a consequence of illness, gastric feeding, or intentional elevation of gastric pH), and thus, when aspiration occurs, gram-negative organisms and *S. aureus* can be commonly recovered when a PSB has been used to collect samples (35). When aspira-

TABLE 1  
PATIENTS WITH MILD-TO-MODERATE HAP, NO UNUSUAL RISK FACTORS, ONSET ANY TIME OR PATIENTS WITH SEVERE HOSPITAL-ACQUIRED PNEUMONIA WITH EARLY ONSET\*

Core Organisms	Core Antibiotics
Enteric gram-negative bacilli (Non-Pseudomonal)	Cephalosporin
<i>Enterobacter</i> species	Second generation
<i>Escherichia coli</i>	or Non-pseudomonal third generation
<i>Klebsiella</i> species	Beta-lactam/beta-lactamase inhibitor combination
<i>Proteus</i> species	If allergic to penicillin
<i>Serratia marcescens</i>	Fluoroquinolone
<i>Hemophilus influenzae</i>	or Clindamycin + aztreonam
Methicillin-sensitive <i>Staphylococcus aureus</i>	
<i>Streptococcus pneumoniae</i>	

\* Excludes patients with immunosuppression.

TABLE 2  
PATIENTS WITH MILD-TO-MODERATE  
HOSPITAL-ACQUIRED PNEUMONIA WITH  
RISK FACTORS, ONSET ANY TIME\*

Core Organisms Plus:	Core Antibiotics Plus:
Anaerobes (recent abdominal surgery, witnessed aspiration)	Clindamycin or beta-lactam/beta-lactamase inhibitor (alone)
<i>Staphylococcus aureus</i> (coma, head trauma, diabetes mellitus, renal failure)	+/- Vancomycin (until methicillin-resistant <i>Staphylococcus aureus</i> is ruled out)
<i>Legionella</i> (high-dose steroids)	Erythromycin +/- rifampin†
<i>Pseudomonas aeruginosa</i> (prolonged ICU stay, steroids, antibiotics, structural lung disease)	Treat as severe hospital-acquired pneumonia (Table 3)

\* Excludes patients with immunosuppression.

† Rifampin may be added if *Legionella* species is documented.

tion of gastric contents occurs, it is often difficult to distinguish a bacterial pneumonia from a chemical (noninfectious) pneumonitis.

Other risk factors for anaerobic HAP include recent thoraco-abdominal surgery or the presence of an obstructing foreign body in the airway. Careful efforts to culture anaerobes from the respiratory secretions of patients with HAP confirm that these organisms are present in about a third of patients, although these findings have not been consistent in all studies and their clinical significance is debated (31). Many patients commonly recover from HAP without receiving specific anti-anaerobic therapy, and even if anaerobes are part of the polymicrobial flora of a mixed infection, this flora often includes at least one other, usually more pathogenic, aerobic bacterial species (31).

Additional pathogens should be added to the list of core organisms as potential etiologic agents if other risk factors are present (Table 2). For example, *S. aureus* (usually methicillin-sensitive, unless the patient has received antibiotics before HAP onset) is a common pathogen in patients who have coma, head injury, recent influenza, a history of intravenous drug use, chronic renal failure, or diabetes mellitus (37). If pneumonia develops after the patient has had a prolonged hospital stay or after the use of antibiotics (for any reason), there is an increased likelihood of infection with MRSA (38), as well as resistant gram-negative organisms, including *P. aeruginosa*, *Enterobacter* spp., and *Acinetobacter* spp. (39, 40). Corticosteroids predispose to infec-

TABLE 3  
PATIENTS WITH SEVERE HOSPITAL-ACQUIRED  
PNEUMONIA WITH RISK FACTORS, EARLY ONSET  
OR PATIENTS WITH SEVERE HAP, LATE ONSET\*

Core Organisms, Plus	Therapy
<i>P. aeruginosa</i> <i>Acinetobacter</i> species Consider MRSA	Aminoglycoside or ciprofloxacin  plus one of the following: Antipseudomonal penicillin Beta-lactam/beta-lactamase inhibitor Ceftaridime or ceftoperazone Imipenem Aztreonam† +/- Vancomycin

\* Excludes patients with immunosuppression.

† Aztreonam efficacy is limited to enteric gram-negative bacilli and should not be used in combination with an aminoglycoside if gram-positive or *Hemophilus influenzae* infection is of concern.

tion with *Legionella* spp., *P. aeruginosa*, and *Aspergillus* spp. (41, 42). When a combination of risk factors are present, the spectrum of potential pathogens broadens to include the same organisms as are seen with severe HAP (Table 3) (30, 32-34).

Although corticosteroids can increase the risk of HAP with *P. aeruginosa* and fungi (particularly *Aspergillus* spp.) (42), they also serve as an important risk factor for nosocomial *Legionella* infection in some geographic regions. In one study, 22 cases of nonepidemic *Legionella* infection were identified among 286 episodes of HAP (41), and risk factors included malignancy, renal failure, neutropenia, corticosteroid therapy, and cytotoxic chemotherapy. Factors such as altered consciousness, prior antibiotic therapy, and intubation that were known to be associated with other types of pneumonia had a negative association with *Legionella* infection (41).

Nosocomial Legionnaires' disease results from inhalation of organisms into the lung from a source in the environment (usually a contaminated hospital water system), although aspiration from a colonized oropharynx may also play a role (43). As many as 60% of reported cases occur in patients who are immunocompromised (41), but not all hospitals have patients with this infection, suggesting that the disease may occur in specific geographic pockets. However, if HAP from *Legionella pneumophila* is documented, an epidemic is possible, and surveillance for cases should be undertaken after an index case is identified.

#### Severe HAP

Although there are very few studies that have defined severe HAP, the definitions developed for use in patients with community-acquired pneumonia can be extended to this population and are listed in Table 4 (13). Severe HAP may occur either in patients already residing in the ICU, especially patients receiving mechanical ventilation, or it may precipitate admission to the ICU. Severe HAP may result from the presence of specific risk factors, which are usually multiple, or from the virulence of the infecting agent. Although core organisms are frequently isolated in this setting, additional pathogens also need to be considered, especially if the patient has been hospitalized for  $\geq 5$  d or if specific risk factors are present.

When severe HAP occurs within  $< 5$  d of admission in patients without risk factors for specific pathogens, the patient is likely to be infected by the core organisms (Table 1) (34). The most common settings occur after a major elective operation, emergency surgery, or an acute and serious medical event (myocardial infarction, cerebral vascular accident). The core organisms of particular concern are *H. influenzae* and methicillin-sensitive *S. aureus*, but not highly resistant EGNB, *P. aeruginosa*, or *Acinetobacter* spp. In one study of 91 episodes of ventilator-associated pneumonia (VAP), *H. influenzae* was recovered from the PSB samples of 20 patients, especially those who had not received prior antibiotic therapy and did not have a prolonged hospital stay (44). With time, the spectrum of organisms coloniz-

TABLE 4  
DEFINITION OF SEVERE HOSPITAL-ACQUIRED PNEUMONIA

Admission to the intensive care unit
Respiratory failure, defined as the need for mechanical ventilation or the need for $> 35\%$ oxygen to maintain an arterial oxygen saturation $> 90\%$
Rapid radiographic progression, multilobar pneumonia, or cavitation of a lung infiltrate
Evidence of severe sepsis with hypotension and/or end-organ dysfunction:
Shock (systolic blood pressure $< 90$ mm Hg, or diastolic blood pressure $< 60$ mm Hg)
Requirement for vasopressors for more than 4 h
Urine output $< 20$ ml/h or total urine output $< 80$ ml in 4 h (unless another explanation is available)
Acute renal failure requiring dialysis

ing the oropharynx is likely to change, favoring increased rates of colonization by EGNB such as *Klebsiella* spp., *Proteus* spp., *Serratia* spp., and *E. coli* (14, 34, 40).

If the patient develops severe HAP after being hospitalized for  $\geq 5$  d, the most commonly encountered pathogens are those listed in Table 3. The pathogens listed include the core organisms plus highly resistant gram-negative bacteria, such as *P. aeruginosa* and *Acinetobacter* spp. In some studies MRSA has been identified in this population of patients as well (38). This same spectrum of bacteria also should be considered if risk factors are present, even if the severe HAP is early onset.

The relationship between *S. aureus* and specific risk factors for HAP has been documented in a number of studies. In one study 13 of 50 patients with VAP had *S. aureus*. The risk factors included: age  $< 25$  yr, recent trauma, no corticosteroid therapy, and coma, with coma persisting as the only relevant risk factor in a multivariate analysis (37). In a similar study of 161 patients with multiple trauma, the investigators observed an association between *S. aureus* pneumonia and coma on admission, with this organism being found in 55.8% of pneumonia patients who had a Glasgow coma score  $< 9$  for at least 24 h after admission (45). If *S. aureus* is being considered a potential pathogen, it is necessary to know the institution-specific prevalence of methicillin-resistant organisms before the selection of an antimicrobial agent. Infection caused by methicillin-resistant organisms is more likely if patients have received antibiotics before the onset of pneumonia (38).

Patients with severe HAP (Table 3) are at risk for potentially resistant organisms for several reasons. First, they may have received certain therapeutic interventions that predisposed to infection with virulent gram-negative bacteria or they may have a number of severe coexisting host impairments that allow such organisms to infect them (46). In addition, the presence of certain organisms, such as *P. aeruginosa*, can lead to severe pneumonia, or a patient may become severely ill because of the presence of a resistant pathogen that has become established as the result of ineffective therapy with a more standard antibiotic regimen.

In the intensive care setting, approximately one third of patients receive mechanical ventilation (47). The bacteriology of VAP can be polymicrobial in up to 40% of cases (7). In this population, patients who have received antibiotics before the onset of pneumonia are especially likely to be infected by *P. aeruginosa* or *Acinetobacter* spp. (33, 39). In one study of 129 episodes of VAP diagnosed by PSB (39), patients exposed to antibiotics before the onset of pneumonia had gram-negative bacilli, accounting for 69% of all episodes, and more than half of these cases involved *P. aeruginosa*. Other risk factors for pneumonia due to *P. aeruginosa* include corticosteroid therapy, malnutrition, structural lung disease (bronchiectasis, cystic fibrosis), prolonged hospitalization, and mechanical ventilation (40). When a resistant gram-negative organism causes pneumonia, particularly when it is acting as a superinfection, mortality is increased (39, 48). The "attributable mortality" of VAP due to *P. aeruginosa* or *Acinetobacter* spp. is greater than that of other types of VAP (7, 8).

#### DIAGNOSTIC STUDIES IN PATIENTS WITH HOSPITAL-ACQUIRED PNEUMONIA

Diagnostic testing is ordered for three purposes: (1) to determine if a patient has pneumonia as the explanation for a new constellation of signs and symptoms; (2) to identify the etiologic pathogen, when pneumonia is present; and (3) to define the severity of illness. Unfortunately, clinical and bacteriologic tools cannot always reliably provide this information. Diagnostic strategies for HAP range from using a clinical approach to the incorpora-

tion of invasive microbiologic techniques. Controversy persists about which approach and specific methods are preferable and most effective (11, 12). When the clinical approach is used, pneumonia is defined by the presence of a new lung infiltrate plus clinical evidence that the infiltrate is of an infectious origin. This evidence includes the new onset of fever, purulent sputum, or leukocytosis. In this setting, the etiologic diagnosis is made by culturing transtracheal aspiration, blood, and any available pleural fluid. Tracheal aspirate and sputum cultures can give a specific etiologic diagnosis of pathogens such as *M. tuberculosis* or *Legionella* spp. Invasive microbiologic techniques employ either protected to unprotected sampling methods to collect lower airway specimens for quantitative culture. These methods usually are confined to intubated patients, often requiring an invasive procedure (usually bronchoscopy with PSB and/or BAL), and both the presence of pneumonia and the etiologic pathogen are determined by whether the respiratory tract specimen contains organism(s) above a predetermined threshold concentration.

No diagnostic approach is without problems. The clinical approach may be overly sensitive, and patients can be treated for pneumonia when another nonpulmonary infection or noninfectious process is present. Not all patients with a clinical diagnosis of HAP actually have lower respiratory tract infection, and many noninfectious processes may lead to lung infiltrates and fever. Processes that may mimic pneumonia include: congestive heart failure, atelectasis, pulmonary thromboembolism, drug reactions, pulmonary hemorrhage, and adult respiratory distress syndrome (ARDS). Invasive microbiologic techniques have a different set of problems, including the cost of the procedure, the need for a specialized laboratory and specific clinical skills, the possibility that results may not be accurate if the patient is receiving antibiotics at the time of testing, and the concern that these methods may not be sensitive enough to diagnose all cases of HAP, especially early forms of infection (11).

Regardless of the approach chosen, all patients with suspected HAP required certain diagnostic evaluations. A careful history and physical examination can define the severity of HAP (Table 4). In addition, the presence of the specific conditions (Table 2) can have an impact on the likely etiologic pathogens. All patients should also have a chest radiograph (preferably PA and lateral), and two sets of blood cultures from separate sites. The chest radiograph can be used to define both the presence and location of infiltrates and the severity of the pneumonia by the presence of multilobar, rapidly spreading, or cavitary infiltrates. The chest radiograph can also identify complications such as pleural effusion. Blood cultures have both diagnostic and prognostic value and can isolate the etiologic pathogen in 8% to 20% of all patients with HAP, defining a population at increased risk for a complicated course if the results are positive (10). When blood cultures do isolate a pathogen, it is important to exclude other sites of infection. In patients with severe HAP, an additional source of infection is present in up to 50% of patients with positive blood culture (7, 10).

All patients should have an arterial blood gas or oximetry to help define the severity of illness and to determine the need for supplemental oxygen. Other laboratory studies (complete blood count, serum electrolytes, renal and liver function) can document the presence of multiple organ dysfunction and thus help define the severity of illness, but are not of benefit in identifying a specific pathogen.

A diagnostic thoracentesis to rule out a complicating empyema should be performed if the patient has a parapneumonic effusion, especially if the effusion is  $> 10$  mm on a lateral decubitus film or if the patient appears toxic. The routine examination of this fluid should include measurement of protein, LDH, and glucose (with comparison to serum values obtained at the time of thoracentesis), as well as complete blood cell count and differen-

tial and pH. Gram's stain and acid-fast stain of the pleural fluid sample and cultures for bacteria, fungi, and *M. tuberculosis* should also be obtained.

Serologic studies are of little use in the initial evaluation of patients with HAP and should not be routinely performed. They are occasionally of epidemiologic value and sometimes are helpful for retrospective confirmation of a suspected diagnosis, primarily in viral and *Legionella* infections. There are currently few tests that directly measure specific microbial antigens that are of benefit in the initial evaluation of patients with HAP. However, *S. pneumoniae* and *Legionella* spp. antigens can be measured in specific circumstances. There is considerable interest in this area and, in the future, methods employing monoclonal antibodies, DNA probes, or polymerase chain reaction amplification may provide accurate diagnosis from clinical samples (49, 50).

The value of examining lower respiratory secretions with Gram's stain and the utility of culturing sputum in patients with suspected HAP is limited and results must be interpreted cautiously, with a full knowledge of how the specimen was collected and of the status of the patient at the time of collection. Little reliable data exist regarding the interpretation of Gram's stain and culture of expectorated sputum in HAP (51). By analogy, in community-acquired pneumonia, the usefulness of Gram's staining of expectorated sputum is uncertain, as is the routine collection of bacterial cultures of sputum (13). Direct staining of sputum for acid-fast organisms and fungi and direct fluorescent antibody (DFA) staining for specific *Legionella* spp. provides more specific information and can be diagnostic when positive. For the nonintubated patient, the mean value of sputum culture is to identify the antibiotic sensitivity patterns of the organisms present when resistant pathogens are expected, recognizing that culture of expectorated sputum is neither sensitive nor specific for identifying the etiologic pathogen of HAP.

In the intubated patient with suspected HAP, lower airway secretions are easily obtainable with routine endotracheal aspiration (ETA). Several studies have examined the utility of ETA specimens in patients with VAP. In one study of VAP, a negative Gram's stain of ETA material suggested that pneumonia was not a cause of lung infiltrates and fever (52). Additionally, nonquantitative ETA cultures are a sensitive, but not specific method for evaluating the lower airway microflora (46, 51, 53-55). Because hospitalized patients are commonly colonized by the same types of bacteria that cause HAP, the mere recovery of a potential pathogen from an endotracheal aspirate cannot determine whether the organism is a pathogen or simply colonizing the lower respiratory tract. Most studies have shown that when VAP is present, the etiologic pathogen(s) are usually contained in the ETA, although the predominant organism may not be defined and additional colonizing organisms may also be present (51, 53-55). Thus, nonquantitative ETA cultures can allow the clinician to exclude certain pathogens (significant negative predictive value); and this may be helpful when modifying initial empiric antibiotic therapy, once culture results are available. In addition, ETA cultures can give information about the antimicrobial sensitivity of the isolated organisms, which can then be used to evaluate the potential effectiveness of any empiric antibiotic regimen that has been selected. Quantitative and semiquantitative bacteriology of ETA samples has also been used with promising results, but the technique for obtaining such specimens has not been standardized, and the concentration of recovered bacteria that is diagnostic of pneumonia has not yet been established (53, 54).

The role of quantitative invasive diagnostic techniques in the evaluation of patients with clinical evidence of HAP remains controversial. Questions regarding who should be tested and how frequently invasive sampling should be performed on a patient as well as concerns about accuracy remain to be resolved. In

selected centers, fiberoptic bronchoscopy is employed to obtain lower respiratory tract secretions, usually from intubated patients, using PSB and/or BAL (56, 57). Bacterial growth in these specimens is then quantitated and the presence of pneumonia and the identity of the etiologic pathogen(s) are defined by the recovery of bacteria above a predetermined threshold concentration (PSB > 10<sup>3</sup> and BAL > 10<sup>4</sup> or 10<sup>5</sup> colony forming units [CFU]/ml) (58).

The use of a specific threshold to define the presence of pneumonia does not take into account the fact that lung infection occurs along a bacteriologic continuum; thus, when pneumonia begins or if infectious bronchiolitis is present, the diagnostic threshold may not be met (28, 59). In addition, false-negative results are common if the patient has received antibiotic therapy before invasive testing. Another limitation to invasive diagnostic procedures is the importance of rigorous adherence to technique and expertise in performing bronchoscopic procedures as well as the need for complex laboratory support for quantitative culturing. The results can be influenced by variability of the sampling methods themselves (11). A recent meta-analysis has investigated whether a single diagnostic threshold can be applied to all subgroups of patients (60). Results from this analysis suggest that use of a predetermined threshold concentration for either PBS or BAL may not be appropriate in all clinical settings and that incorporating the clinical likelihood of pneumonia into the evaluation could significantly improve sensitivity and specificity of these tests. Even when invasive methods are used, results are delayed until growth of the quantitative cultures has occurred and, therefore, initial therapy is, by necessity, empiric. Most of these studies have been performed in ventilated patients, and there is less information regarding the role of quantitative microbiological testing in patients with mild-to-moderate HAP.

In some centers, material obtained by PSB or BAL is evaluated by Gram's stain to determine the presence of bacteria, and the finding of organisms, particularly in an intracellular location (in > 2% of alveolar cells), has been found to be predictive of a quantitative culture result above the diagnostic threshold for pneumonia as well as histologic evidence of pneumonia (58, 61). These procedures may be helpful in selected circumstances, such as the work-up of patients not responding to antimicrobial therapy where resistant organisms, other pathogens (i.e., *M. tuberculosis*, fungi), or bronchial obstruction may be present. However, there has not yet been a study to show whether mortality, morbidity, or any other outcome of patients with VAP can be improved if invasive methods are used in place of the clinical diagnosis of VAP.

## ANTIBIOTIC TREATMENT OF HOSPITAL-ACQUIRED PNEUMONIA

### General Approach

Once the clinical decision has been made to initiate therapy for suspected HAP, antibiotic selection should be guided by placing the patient into one of the categories listed in Tables 1-3, according to the algorithm in the Figure. The antimicrobial spectrum of activity, pharmacokinetic profiles, and adverse effects of individual drugs were carefully reviewed by the consensus committee, and the role of monotherapy versus combination drug therapy was considered as well. Whenever possible, antibiotic recommendations were based on well-designed, controlled clinical trials. When such data were not available, then the spectrum of antimicrobial activity, pharmacokinetic data, and reported clinical experience were taken into account. These initial empiric therapy choices may require modification once results of respiratory tract or blood cultures become available.

In classifying patients into one of the categories in Tables 1-3,

it is necessary to define the severity of illness as either mild-to-moderate or severe (Table 4) (13). Patients with mild-to-moderate illness, regardless of when pneumonia occurs, will fall into the descriptions in Tables 1 or 2, depending on the absence (Table 1) or presence (Table 2) of specific risk factors for infection. Patients with severe HAP, usually requiring admission to the intensive care unit, will fall into the descriptions in Tables 1 or 3. Treatment regimens will depend on whether the patient was previously healthy and developed HAP early, within < 5 d of hospitalization (Table 1), or if either specific risk factors are present or HAP occurred  $\geq$  5 d after hospitalization (Table 3). The **regimens listed** in Table 3 for severe HAP are directed at particularly virulent and/or drug-resistant organisms. In such cases initial antibiotic treatment relies on combination chemotherapy to provide a broader spectrum of coverage as well as possible additive or even synergistic activity against such pathogens.

#### Antibiotic Issues

Several specific issues relating to antibiotic selection were considered, including the expected efficacy of an appropriate therapeutic choice. As has been discussed, the attributable mortality of HAP is **33%–50%**, implying that at least half of all patients who die do so for reasons other than pneumonia, and these patients would not be expected to survive an episode of HAP, even with appropriate antimicrobial therapy. The magnitude of benefit of antibiotics in HAP patients who are not dying from other causes is also uncertain. One study of patients with ARDS suggested that when patients developed either pulmonary or **extrapulmonary** infection, the outcome was uniformly poor, regardless of whether appropriate antibiotic therapy was selected (62). Several more recent studies dealing specifically with HAP have shown that the use of appropriate antimicrobial therapy can improve outcome, with survival rates reaching **70%–80%** (5, 63, 64).

Specific pharmacologic features of antimicrobial **agents** should also be considered, including cost. Adequate studies **defining** the cost of antibiotics in patients with HAP have not been performed, and these studies need to incorporate outcome as well as acquisition costs of the antimicrobial agents. The penetration of antibiotics to the site of infection is important, but it remains unclear whether concentrations in bronchial secretions or in **epithelial** lining fluid are most relevant for predicting efficacy in patients with pneumonia (65). Some agents penetrate into respiratory secretions better than others. Aminoglycosides have relatively poor penetration, while fluoroquinolones can achieve concentrations in bronchial secretions that equal or exceed serum levels (65,66). Because of these considerations, an **aminoglycoside** should never be used alone in the treatment of a **gram-negative** lung infection (66). In addition to concerns about **low** lung concentrations, it is possible for aminoglycosides to be inactivated in the acid **pH** environment of the pneumonic lung.

Consideration of bactericidal mechanisms may also be relevant in antibiotic selection and dosing. Agents such as the **aminoglycosides** and quinolones are bactericidal in a concentration-dependent fashion, killing more rapidly at high concentrations (67). In addition, these agents have a prolonged postantibiotic effect (PAE), allowing them to suppress bacterial growth even after the antibiotic concentration is below the minimal inhibitory concentration of the target organism (67). Other agents, such as vancomycin and the beta-lactams, are also bactericidal but in a time-dependent (time above the organisms' minimal inhibitory concentration) rather than in a concentration-dependent fashion. No PAE, or a very short PAE against gram-negative bacilli, is seen with beta-lactam antibiotics (penicillins, **cephalosporins**, aztreonam). One exception is the beta-lactam **carbapenem** antibiotics (such as imipenem), which have shown a PAE against gram-negative bacilli such as *P.aeruginosa* (67).

These pharmacodynamic effects may lead to specific dosing regimens, and this concept is best illustrated with once daily aminoglycoside therapy (68). When the entire daily dose of aminoglycoside is administered once every 24 h, there is a high peak concentration and a low trough concentration, which could maximize efficacy by taking advantage of both the concentration-dependent killing mechanism and the prolonged PAE of this type of agent while minimizing toxicity. In clinical trials these goals have been achieved with varying degrees of success (69, 70).

#### Specific Antibiotic Regimens

Patients without unusual risk factors who present with mild-to-moderate HAP with onset at any time or severe HAP of early onset will likely be infected by the core organisms that are listed in Table 1. These include nonpseudomonal gram-negative bacilli (*Klebsiella* spp., *Enterobacter* spp., *E.coli*, *Proteus* spp., *Serratia* spp.), methicillin-sensitive *S.aureus*, *H.influenzae*, and *Streptococcus* spp., including *S.pneumoniae*. Monotherapy is usually appropriate in this setting, using agents such as a second-generation cephalosporin (e.g., cefuroxime), a nonpseudomonal **third-generation** cephalosporin (e.g., cefotaxime or ceftriaxone), or a beta-lactam/beta-lactamase inhibitor combination (ampicillin/sulbactam, ticarcillin/clavulanate, or piperacillin/tazobactam). If the likely pathogen is an *Enterobacter* spp., (e.g., *E.cloacae* or *E.pantoaea*, formerly *E.agglomerans*) and a third-generation cephalosporin is used, it should be combined with another agent, because of the possibility of *in vivo* induction of beta-lactamase production, regardless of *in vitro* susceptibility data (71).

If the patient is allergic to penicillin, ciprofloxacin can be used, provided that *S.pneumoniae* is not believed to be a concern. Other fluoroquinolones may have improved gram-positive coverage, but large-scale studies in HAP have not been performed using the newer fluoroquinolones. Combination therapy using **clindamycin** and aztreonam can also be used in patients allergic to penicillin, even though aztreonam is a beta-lactam agent, and this regimen can achieve a similar spectrum of antimicrobial activity. Until more data are available to suggest otherwise, it is appropriate to begin therapy intravenously, even with mild illness, although an early switch to oral therapy can be done in responding patients. Studies with fluoroquinolones have shown that an early switch to oral therapy is safe and effective, possibly because these agents can achieve high serum and tissue levels after oral administration (72).

If patients with specific risk factors present with mild-to-moderate HAP, occurring any time during hospitalization, certain additional bacteria, beyond the core organisms should be considered, as noted in Table 2. All of these patients should be treated for the core organisms, and thus, the same drugs listed in Table 1 may be used, but usually they require the addition of other antimicrobial agents to provide coverage for other likely pathogens because of the specific risk factors that are present. For example, clindamycin or metronidazole are active against anaerobes and can be added to the core antibiotics in witnessed or suspected cases of gross aspiration, although a **beta-lactam/beta-lactamase** inhibitor combination agent may be sufficient by itself.

Although *S.aureus* is an important pathogen and is one of the core organisms, the risk of infection with this organism is a particular concern in patients with diabetes, coma, head injury, renal failure, or recent influenza (37, 38, 45). In these settings, additional antibiotic coverage with vancomycin should be considered until a methicillin-resistant organism is excluded. MRSA is a particular concern if the organism is endemic to an institution or if the patient has been treated with antibiotics before the onset of pneumonia. If the patient has received high-dose corticosteroids and is not intubated when **pneumo-**

nia develops, *Legionella* infection is possible, especially in certain geographic regions or institutions, and a macrolide (such as erythromycin) can be considered in addition to therapy directed at the core organisms (41). When multiple risk factors are present, particularly if the patient has had prolonged hospitalization, prior antibiotics, or a long stay in the ICU (even for non-respiratory illness), then highly resistant gram-negative bacilli, including *P. aeruginosa* and *Acinetobacter* spp., become a concern, and even with mild-to-moderate illness, the patient should be treated according to the regimens listed in Table 3.

When an individual has severe HAP, either of early onset with risk factors or with late onset (Table 3), treatment should be directed against the core organisms as well as against more resistant and virulent gram-negative bacilli, such as *Acinetobacter* spp., and *P. aeruginosa*. This requires the use of combination antimicrobial therapy. Drugs that are active against *P. aeruginosa* include: the antipseudomonal penicillins (piperacillin, azlocillin, mezlocillin); some third-generation cephalosporins (ceftazidime, cefoperazone); the monobactam, aztreonam; the carbapenem, imipenem; an antipseudomonal beta lactam/beta lactamase inhibitor combination; the aminoglycosides; and a fluoroquinolone, ciprofloxacin. In some severely ill patients, MRSA is also a concern, a vancomycin should also be considered for these individuals.

Although all patients who are treated with the regimens listed in Table 3 should initially receive a combination of antimicrobial agents, some may be able to complete therapy using only a single agent. The decision to continue combination therapy can be made after 2 to 3 d, based on the patient's clinical response and the results of pertinent cultures. If *P. aeruginosa*, resistant *Acinetobacter* spp., or MRSA have not been isolated and the patient is improving, it might be reasonable to change to monotherapy, because there are good data to show the efficacy of monotherapy, even in severe nonpseudomonal HAP (73). Combination therapy is expensive and exposes the patient to multiple toxicities, thereby increasing the risk of antibiotic-associated complications. However, it does have benefits in some patients with HAP, leading to enhanced survival if bacteremic *P. aeruginosa* infection is present (64), and possibly a reduced likelihood of resistance emerging during therapy for all pneumonias due to *P. aeruginosa*. Thus, if *P. aeruginosa* is identified, treatment with a combination regimen should continue. However, even combination therapy may not prevent the emergence of resistance, and one recent study showed similar rates of *P. aeruginosa* resistance whether HAP patients were treated with imipenem alone or with imipenem plus the aminoglycoside, netilmicin (74). Whether these findings are specific for the antibiotics used in the study or for *P. aeruginosa* in general is unclear. Similarly, if *Enterobacter* spp., are isolated and a third-generation cephalosporin is being used, then combination therapy also should be continued with an aminoglycoside or fluoroquinolone to prevent the emergence of resistance (71).

Monotherapy has been studied in patients with HAP who were not severely ill and has been successful, but few studies have examined its efficacy in patients who are severely ill (30, 66, 75, 76). In one recent study of 405 patients with 78% having severe HAP as defined by the criteria listed above, monotherapy with imipenem was compared with monotherapy with ciprofloxacin (73). Both monotherapy regimens were effective if *P. aeruginosa* was not present (approximately 70% of the patients), but therapy with ciprofloxacin was associated with a better clinical response and an enhanced rate of eradication of *Enterobacter* spp. (73). Monotherapy with either agent was not effective in eradicating the majority of *P. aeruginosa* infections, and resistance commonly developed during therapy. These findings support the conservative approach of starting patients with severe HAP on combination antipseudomonal therapy, which might prevent the

emergence of resistance if *P. aeruginosa* is isolated. However, the findings also support the practice of streamlining to monotherapy with certain selected antibiotics, even in patients with severe HAP, if *P. aeruginosa* or other potentially resistant pathogens are not present, showing that such an approach is likely to be both safe and effective.

When combination antipseudomonal therapy is used, several approaches are possible. The first is a combination of a beta-lactam with an aminoglycoside, which can achieve synergy *in vitro* against *P. aeruginosa*, although the occurrence of synergy *in vivo* is uncertain (77). This uncertainty is based on both the possible inactivation of aminoglycosides in the acidic environment of infected endobronchial areas and the poor penetration of these agents into lung tissue (78). A second choice is the use of two beta-lactam agents, but this combination will not achieve synergy; there is the additional possibility of antagonism between the two agents as well as the induction of beta-lactamases, which might inactivate one or possibly both beta-lactam agents simultaneously. Another way to combine agents is to use a beta-lactam with ciprofloxacin. Such combinations may provide additive or possibly even synergistic activity against pathogens and will have the advantage of good parenchymal penetration of the fluoroquinolone, along with a reduced potential for toxicity, when compared with the aminoglycosides (79).

#### Duration of Antibiotic Therapy

Prospective studies assessing optimal duration of antibiotic therapy for HAP have not been reported. Duration of therapy should be individualized, depending on the severity of illness, rapidity of clinical response, and infecting pathogen. Microorganisms such as *P. aeruginosa* or *Acinetobacter* spp. have been associated with high rates of treatment failure, relapse, and death (7, 8, 80). The presence of multilobar involvement, malnutrition, severe debilitation, cavitation, or a necrotizing gram-negative bacillus (GNB) pneumonia may be associated with delayed and often incomplete resolution. While carefully controlled studies documenting duration of therapy have not been reported, in these settings antibiotics should be continued for a minimum of 14-21 d to reduce the chance of relapse. By contrast, cure rates exceeding 95% have been noted for HAP caused by methicillin-sensitive *S. aureus* or *H. influenzae*; for these pathogens, a 7-10 d course of therapy may be adequate (30, 44). Substituting an oral antibiotic may be appropriate, provided the organism is susceptible *in vitro*, clinical improvement has occurred, and adequate oral absorption can be assured. In this context, the oral fluoroquinolones provide broad spectrum coverage, achieve high levels in bronchopulmonary secretions, and may reduce hospital costs (81).

#### RESPONSE TO THERAPY

After the institution of empiric therapy, antibiotic choices may need to be modified once the results of blood or respiratory tract cultures become available. This may be necessary because a resistant or unsuspected pathogen was found or because an anticipated organism (such as *P. aeruginosa* and *Acinetobacter* spp.) was not recovered. Even without such situations, it may be necessary to modify therapy and reevaluate the patient because of a failure to respond to the initial empiric regimen. Critical to the routine use of any of the proposed empiric antibiotic regimens is the ability to recognize when a patient is not responding appropriately. Unfortunately, there is a general lack of information about the natural course of HAP resolution. In addition, because of the variability in diagnosing the infection, the natural history of presumed HAP may differ, depending on what disease process is actually present in a given patient. Clinical response may also be related to patient factors (such as age and

comorbidity), bacterial factors (such as antimicrobial resistance patterns and virulence), and other events that may occur during the course of HAP.

#### Defining Normal Pattern of Resolution

Resolution of HAP can be defined either clinically or microbiologically. Clinical end points such as improvement, resolution, delayed resolution, relapse, failure, and death can be defined (82). These end points are recognized by following such features as a change in fever, sputum purulence, leukocytosis, or oxygenation radiographic patterns and the resolution of organ failure. Using this approach, clinical improvement is usually not apparent for the first 48-72 h of therapy, and, therefore, the selected antimicrobial regimen should not be changed during this time, unless progressive deterioration is noted or initial microbiologic studies dictate the need to modify therapy.

Appropriate respiratory tract cultures can be used to define microbiologic resolution. Using serial cultures, end points can be defined, such as bacterial eradication, superinfection (infection with a new organism), recurrent infection (elimination, then return, of original organism), or microbiologic persistence. Some investigators have advocated the use of serial quantitative microbiologic studies of lower respiratory tract secretions to define resolution end points (83). In one such study, serial PSB samples, collected 72 h after starting therapy, were used to define the bacteriologic response to therapy, and the results of these microbiologic evaluations were compared with the clinical outcome (83). When the follow-up PSB sample showed no growth or  $<10^3$  CFU/ml, a clinical therapeutic failure occurred only 7% of the time, while a finding of  $>10^3$  CFU/ml, (microbiologic failure to eradicate) was associated with clinical failure in 55.8% of the patients. At present, there are no data showing that the recognition of a microbiologic nonresponse can lead to modifications in therapy that can improve clinical outcome.

Chest radiographs are of limited value for defining clinical improvement in severe pneumonia, and initial radiographic deterioration is common, especially among patients who are bacteremic or who are infected with highly virulent organisms. In addition, radiographic improvement often lags behind clinical parameters, especially in the elderly and in individuals with coexisting disease (eg., COPD). However, the finding of rapidly deteriorating radiographic pattern, with a follow-up chest radiograph showing progression to multilobar involvement, a  $>50\%$  increase in the size of the infiltrate within 48 h, development of cavitory disease, or significant pleural effusion, should raise concern.

In patients with VAP, rapid clinical improvement with extubation occurs in less than 20% of cases (83). This pattern may be more common among patients with less severe HAP and in patients who do not have serious coexisting illnesses. Individuals with advanced age or comorbidity may improve with therapy, but the process may be slow. On the other hand, rapid deterioration can occur in roughly a quarter of VAP cases and mandates an aggressive evaluation (83).

#### Reasons for Deterioration or Nonresolution

There are several possible causes for rapid deterioration or failure to improve. These include the possibility that the process being treated is not pneumonia or that certain host, bacterial, and therapeutic (antibiotic) factors have not been considered.

Many noninfectious processes may be mistakenly labeled as HAP, including atelectasis, congestive heart failure, pulmonary embolus with infarction, lung contusion (in trauma patients), and chemical pneumonitis from aspiration. Patients with ARDS can have fibroproliferative diffuse alveolar damage, while any mechanically ventilated patient can have pulmonary hemorrhage

(84, 85). In one series, 26 of 69 ventilated patients with new lung infiltrate had pulmonary hemorrhage at autopsy, sometimes in association with pneumonia (84).

Host factors associated with a failure to improve during empiric therapy include the presence of any condition that is known to increase the chance of mortality. These include prolonged mechanical ventilation, respiratory failure, an underlying fatal condition, age  $>60$  yr, bilateral radiographic infiltrates, prior antibiotic therapy, prior pneumonia (i.e., the current episode represents superinfection), and/or chronic lung disease (4, 5, 82). In addition, some patients can have clinically unrecognized immunosuppression (e.g., AIDS), and unrecognized *Pneumocystis carinii* pneumonia may be a cause of nonresponse to therapy.

Bacterial variables can also be associated with an adverse outcome of initial therapy. The infecting pathogen can be resistant at the outset to the chosen therapy or can acquire resistance during therapy, particularly if the organism is *P. aeruginosa* that has been treated with a single agent (73, 74). Some organisms are inherently difficult to eradicate, even with effective therapy. In one study of *P. aeruginosa* pneumonia in an ICU, 20 of 34 patients survived an initial episode of infection. However, among 10 of the survivors, recurrent infection developed, as defined by clinical, radiographic, and bacteriologic criteria (80). Certain types of infection are associated with a poor outcome, especially those with gram-negative bacilli, polymicrobial flora, or bacteria that have acquired antibiotic resistance (8, 82). In patients who are mechanically ventilated, infection with *P. aeruginosa* or *Acinetobacter* spp has a particularly high mortality, approaching 90% in some series (7). Finally, pneumonia can be due to other pathogens (i.e. *M. tuberculosis*, fungi, or respiratory viruses) or an unusual bacterial pathogen not included in the initial empiric regimen.

Certain complications during therapy can also lead to an apparent failure to respond to therapy. Some patients with HAP can have other sources of fevers simultaneously, particularly sinusitis, vascular catheter-related infection, pseudomembranous enterocolitis, or urinary tract infections (86, 87). Complications of the original pneumonia can also lead to failure, including development of lung abscess or empyema. Other considerations for persistent fever or pulmonary infiltrates include drug fever, sepsis with multiple system organ failure, or pulmonary embolus with secondary infarction.

#### Evaluation of the Nonresponding Patient

For patients who are deteriorating rapidly or not responding to initial therapy, it may be necessary to broaden antimicrobial coverage while awaiting the results of cultures and other diagnostic studies. An aggressive evaluation is required for this type of individual, starting with a careful differential diagnosis and a repeat sampling of respiratory tract secretions for culture and antimicrobial sensitivity patterns. This can be done by suctioning if the patient is intubated, or by a bronchoscopic procedure with quantitative cultures in both intubated and nonintubated patients. Even though patients in this clinical setting are receiving antibiotics, the recovery of organisms at high concentrations using invasive methods is possible and may indicate that infection with a resistant organism is present. If cultures show a resistant or unusual pathogen, therapy can be modified appropriately. If cultures do not show a resistant or unsuspected pathogen, then consideration of a noninfectious process or of one of the complicating problems discussed previously is appropriate. This necessitates the changing of vascular access catheters and the culturing of blood, line tips that have been removed, and urine, as well as other easily accessible sites.

Specialized radiologic procedures may be helpful in identifying anatomic reasons for failure. Lateral decubitus chest radio-

graphs, ultrasound, or computed tomography (CT) scanning may reveal pleural fluid, which should be evaluated to exclude the diagnosis of empyema. Additionally, CT scanning can separate pleural fluid from parenchymal disease and can demonstrate **pa**-renchymal abscesses, adenopathy, and pulmonary masses. CT scanning of extrathoracic sites may also help to identify other areas of infection, and particular attention should be focused on the abdomen in patients who have ARDS (88). One commonly infected site in patients with nasotracheal or nasogastric tubes in place are the sinuses, and CT scanning can identify **opacifica**-tion or the presence of an air/fluid level in the sinuses. When these findings are present, sinus aspiration and culture may be necessary and may define the presence of infection, which can often coexist with HAP (86). Ventilation perfusion scans or pulmonary arteriography may be needed for selected patients if pulmonary embolus with infarction is likely.

If this microbiologic and radiographic evaluation is negative, a decision should be made whether to observe the patient while either continuing or empirically changing antibiotics or to perform an open lung biopsy. There is debate about the value of open lung biopsy in nonimmunosuppressed patients with suspected HAP. The available evidence does not suggest a clear outcome benefit, and therefore, the decision must be individualized. Bronchoscopy that demonstrates no unusual or resistant organisms, along with an aggressive but unrevealing search for **extrapul**-monary infectious foci, should be done before performing an open lung biopsy. Even if bronchoscopic cultures and other diagnostic testing are not helpful, the decision to perform an open biopsy should be guided by the patient's clinical status. If there has been slow but progressive improvement, close observation alone may be the most appropriate course.

If the patient remains hemodynamically stable but does not show evidence of clinical improvement, and bronchoscopic and radiologic evaluation are unrevealing, an alteration in antibiotics or initiation of anti-inflammatory therapy (corticosteroids) may be appropriate before proceeding with an open biopsy. However, if the patient deteriorates early (within the first 48-72 h of therapy) or has initially improved but then deteriorates, additional antibiotics directed at resistant or "unusual" bacteria can be added while doing an aggressive radiographic and microbiologic evaluation. If these tests are not diagnostic, open lung biopsy could then be performed expeditiously.

#### PREVENTION OF HOSPITAL-ACQUIRED PNEUMONIA

Although there is widespread interest in the prevention of HAP, there are no regimens that are proven to be effective for a wide range of hospitalized patients. A number of preventive strategies have been applied and fall into one of four categories: (1) currently available and probably effective for specific populations and indications; (2) currently available, promising in efficacy, and being used by some hospitals on a regular basis; (3) currently available but of unproven value, being used in investigational studies, or on a limited clinical basis; and (4) unproven regimens, still being evaluated.

##### Regimens with Probable Efficacy for Specific indications

In this category are pneumococcal and influenza vaccination, handwashing, and isolation of patients with multiply resistant respiratory tract pathogens. The efficacy of vaccinations against *S. pneumoniae* and influenza virus in preventing HAP is unknown, but they are effective for preventing respiratory **infec**-tion and hospitalization in specific at-risk populations. Indirectly, by **preventing** respiratory infection and hospitalization, these vaccines may reduce the incidence of HAP, and they represent sound medical care for patients qualifying for the vaccines. **Handwash**-ing between patient contact is a basic and often neglected be-

havior by medical personnel. This simple maneuver can prevent the transfer of pathogens from patient to patient and can keep the hands of medical personnel free of potentially pathogenic bacteria. **Such** "exogenous sources" of organisms can lead to the direct inoculation of organisms into the tracheobronchial tree, and if the tracheobronchial epithelium is able to bind such organisms, colonization and subsequent pneumonia may occur. Similarly, the transfer of resistant pathogens from patient to patient may be prevented by isolating patients with highly resistant organisms such as MRSA. Unfortunately, such "barrier methods" will not be effective in preventing infection with organisms that are part of the critically ill patient's endogenous flora; thus, most gram-negative pneumonias cannot be avoided by isolation methods.

##### Regimens with Probable Effectiveness Used Widely in Some Clinical Settings

The approaches that fit into this descriptive category include nutritional support, attention to the size and nature of the gastrointestinal reservoir of microorganisms, careful handling of ventilator tubing and associated equipment, subglottic secretion drainage, and lateral rotational bed therapy.

Nutritional support is commonly used in hospitalized patients because of the observation that malnutrition can increase the risk of pneumonia. Nonetheless, there is no clear-cut evidence that nutritional support can reduce the risk of HAP. If nutritional support is given, careful attention to the route and volume of feeding, as well as to a number of other methodologic factors, is necessary and may influence the incidence of HAP. When **enteral** nutrition, delivered by a feeding jejunostomy, has been compared with total parenteral nutrition (TPN), it has been associated with a lower incidence of HAP (89). Although the mechanism for this occurrence is unknown, it has been speculated that **enteral** nutrition stimulates the intestinal mucosa, thereby preventing bacterial translocation (a possible mechanism for pneumonia), and that **enteral** nutrition, compared with TPN, changes the synthesis of inflammatory mediators by the liver to a favorable balance for host defense function (89).

The superiority of **enteral** nutrition has been demonstrated with distal **enteral** feeding, while feedings delivered to the stomach may not have the same effect. If feedings are delivered to the stomach, a number of methodologic issues must be considered. These include the effect of the feedings on gastric volume and **pH**, because elevation of either of these variables can expand the size of the gastric bacterial reservoir, which can potentially yield an inoculum of bacteria that could reach the lower respiratory tract. In addition, if patients being fed into the stomach are kept supine rather than semi-erect, pneumonia is more likely (25, 90). With the use of large-bore feeding tubes and **bo**-lus feedings, aspiration may also occur more often than with the use of smaller tubes and continuous feeding methods. One other consideration is the site of feeding tube insertion. One study has shown that the use of orogastric tubes, rather than nasogastric tubes, can reduce the incidence of nosocomial sinusitis, an infection that may lead to subsequent HAP (86).

Although there are no FDA-approved regimens for intestinal bleeding prophylaxis, many critically ill patients receive this intervention, and debate continues about its effect on the incidence of HAP. It is probably too simplistic to say that any intervention that raises gastric **pH** is undesirable, because gastric volume as well as **pH** must be considered, along with some of the other factors already mentioned. In three meta-analyses, the use of sucralfate (which does not increase gastric **pH**) was associated with a reduced incidence of pneumonia, when compared with the use of either antacids alone (which increase both gastric **pH** and volume) or in combination with H-2 antagonists (91-93). However, there is disagreement about whether the use of H-2

**antagonists alone** will lead to a higher rate of pneumonia when compared with sucralfate or placebo. In some recent studies, H-2 blockers did not increase the risk of pneumonia when compared with placebo (92, 94), although the use of sucralfate may reduce the incidence of pneumonia when compared with H-2 antagonists (91, 92). If sucralfate is protective, it may work best for late-onset HAP rather than for early forms of infection (34). The conflicting results with H-2 antagonists may reflect the fact that these agents elevate gastric pH without increasing gastric volume. In addition, many of the analyses have not considered the impact of concomitantly administered gastric feedings. If the goal of nutritional support is to deliver **enteral** feeding into the distal intestine, it may be unnecessary to place a second tube into the stomach just to give sucralfate, and the use of H-2 blockers in patients with small-bowel feeding tubes may be safe. However, antacids should be avoided in patients who are at risk for HAP.

Bacteria can proliferate in respiratory therapy equipment, and the incidence of pneumonia is increased if the tubing is manipulated frequently rather than infrequently (19). Recently, it has been shown that even if ventilator tubing is never changed during the course of mechanical ventilation, the risk of pneumonia is not increased (95). Most hospitals have a policy to change ventilator tubing every 48-72 h, but there are no data to indicate that any particular schedule to tubing changes is likely to reduce the incidence of pneumonia. When tubing is handled, the condensate should always be drained away from the patient, because it can contain large concentrations of bacteria. The use of a heat and moisture exchanger (HME) avoids such condensate and does not seem to add to the risk of pneumonia (96). In-line medication nebulizers should be washed and cleaned after each use to avoid contamination with high levels of bacteria. Closed suction catheters do not appear to alter the incidence of pneumonia but may increase the rate of airway colonization.

In a few medical centers, subglottic secretion aspiration is achieved with the use of a special endotracheal tube, designed with a suction port above the endotracheal tube cuff, in the **subglottic** area. By removing contaminated respiratory secretions before they enter the lung, subglottic secretion aspiration has been reported to reduce the incidence of some types of HAP in **intubated** patients (97). The suctioning can be done intermittently or continuously, and continuous aspiration appears to delay the onset of HAP, preventing early forms of infection (98). This approach cannot prevent infection with organisms that have the capacity to colonize the lung after direct inoculation, and thus, it has not effectively prevented pneumonia caused by *P. aeruginosa* and other forms of late onset HAP (98). Once endotracheal tubes capable of allowing subglottic secretion drainage are more widely available, this approach may be used more regularly.

Lateral rotational bed therapy has been used in both medical and surgical patients and can reduce the incidence of pneumonia in certain populations (99, 100). These include surgical trauma patients and some medical patients, particularly those with sepsis (99, 100). The mechanism for this beneficial effect is unknown but probably relates to mobilization of tracheobronchial secretions. The cost associated with this intervention has limited its widespread use **and** emphasizes the need to apply it to carefully selected patients.

#### Regimens of Unproven Value Used on Limited Investigational or Clinical Basis

**Included** in this category is the selective digestive decontamination (SDD) regimen of topical and systemic antibiotic prophylaxis and topical tracheobronchial antibiotics.

SDD has been studied for many years and involves the use of topical oral and intestinal antibiotics, often with a **systemic** antibiotic added for the first few days of the regimen, with the

goal being the elimination of all potential pathogens from the gastrointestinal tract. With sterilization of "endogenous" bacterial sources, **infection** may be avoided. In the many SDD studies there is a general trend toward reducing the incidence of pneumonia, but this has usually occurred in unblinded studies (101). In blinded studies, the incidence of pneumonia has not always been reduced, particularly if invasive methods were used to define the presence of HAP (102, 103). In general the efficacy of the regimen has been questioned because mortality reduction is often not seen, although one recent analysis suggested a modest reduction in mortality with the use of SDD, provided that systemic antibiotics were included in the regimen (101). Widespread use of SDD has not been adopted because of concerns about the emergence of antibiotic-resistant organisms, the cost of the regimen, and the limited benefit of SDD on mortality. SDD may be effective for specific populations, particularly surgical patients rather than medical patients. More **data** are needed to define the patients who may benefit from this intervention.

Topical antibiotics delivered to the lower respiratory tract alone have been studied and were shown to have no effect on mortality (104). Although this approach was able to reduce the incidence of pneumonia in some studies, it frequently **led** to infection with highly resistant pathogens, and when patients developed pneumonia on this regimen, it was often a fatal event. At the present time this approach cannot be recommended.

#### Unproven Regimens Still Being Evaluated

This category includes the use of biologic response modifiers, **monoclonal** antibodies to specific bacterial antigens, and manipulations of endogenous sources of bacteria by mechanical means. In this latter category is the potential to prevent the **accumulation** of a bacterial biofilm on the endotracheal tube. The endotracheal tube can harbor the growth of large numbers of bacteria along its inner surface, and bacteria at this site will persist in the airway, free from the effect of **antibiotics** and host defenses (27). The development of new biomaterials for endotracheal tubes could lead to the elimination of a tracheal tube biofilm and the eradication of a reservoir of large numbers of bacteria in the airway.

Biologic response modifiers that hold promise for reducing the incidence of HAP are being investigated. These substances are immunomodulators and have the ability to either upregulate or downregulate host defense mechanisms, which in the appropriate setting may have beneficial effects on pulmonary host defenses against invading pathogens. Because extrapulmonary infections have been associated with abnormalities in pulmonary defense mechanisms (105), strategies that effectively reduce the severity of systemic infection (such as sepsis) might be beneficial in lowering rates of secondary HAP. To date, there are no proven interventions that accomplish this goal. Efforts to intervene in the **cytokine/mediator** cascade initiated by gram-negative bacteria and/or lipopolysaccharide, which is thought to be responsible for the deleterious consequences of the sepsis syndrome, are ongoing. Antilipopolysaccharide antibodies (**E5** and HA-IA) have not proved efficacious in improving outcome in patients with gram-negative bacterial sepsis. Ongoing studies of other biologic response modifiers include antibodies to the cytokine tumor necrosis factor, interleukin-1 receptor antagonist, and the cyclooxygenase inhibitor, ibuprofen. Other potential modulators include platelet-activating factor antagonists (106).

Other strategies have been investigated to accelerate the resolution of pneumonia after it is acquired **and** to prevent the development of pneumonia. Passive immunization with **hyperimmune** anti-pseudomonas immune globulin for patients with documented *P. aeruginosa* pneumonia has failed to result in any benefit in mortality rates or length of hospital stay. The cytokine **granulocyte** colony-stimulating factor (G-CSF) is a hematopoietic

cytokine that enhances both the number and function of circulating neutrophils. Preclinical evaluations in models of infection and results of trials in neutropenic oncologic patients show beneficial effects of G-CSF in hastening the resolution and preventing the acquisition of infections. A recent trial has shown that the administration of G-CSF is safe in patients with **community-acquired pneumonia (107)**, and a randomized prospective trial is under way to determine therapeutic efficacy in patients presenting with moderately severe community-acquired pneumonia.

Another cytokine of potential utility in preventing pneumonia or accelerating its resolution is interferon-gamma (IFN). While systemically administered IFN is not always effective in models of sepsis or in patients at risk for sepsis (108), local administration into the lung appears effective in decreasing the burden of infecting organisms and augmenting local host defenses in several animal models of pneumonia (109). Aerosol administration of IFN to normal **humans** results in activation of the alveolar **macrophage**, without concurrent activation of systemic mononuclear cells (110). IFN remains a potential therapeutic modality for bacterial and nonbacterial pathogens in the lung, and clinical investigations will likely proceed in the near future.

Thus, while there are no proven modalities for **immunoprophylaxis** of HAP, investigations are ongoing with biologic response modifiers as both preventive and therapeutic strategies in this disease setting. It is possible that single agents or combinations thereof, alone or in conjunction with available antibiotics, may prove effective in reducing the mortality or morbidity of HAP.

#### SUMMARY AND RECOMMENDATIONS

HAP remains a common problem and is the number one cause of death from nosocomial infection. Our knowledge of HAP is incomplete, and controversies surrounding diagnosis, treatment, and prevention continue. Even without answers to all important **issues**, it is necessary to have a logical approach to the initial management of HAP in the nonimmunocompromised patient. This document provides information about the **pathogenesis**, microbiology, diagnosis, treatment, and prevention of HAP. The therapeutic algorithms are empiric and are initiated after the clinician's criteria for diagnosing lung infection have been satisfied. When using empiric therapy, it is important to recognize nonresponding patients, and an approach to these difficult individuals is also presented.

The initial empiric therapy of HAP is directed at the core organisms common to all patients, but additional bacteria are targeted if other factors are present. Modifications to the expected microbiologic spectrum may be necessary after an assessment of three factors: (1) How severely ill is the patient? (2) Are there any conditions present that can lead to infection with specific pathogens? (3) How long has the patient been hospitalized before development of HAP? Once these assessments have been made, patients are stratified into one of three groups, as shown in the Figure. Each group has a list of likely pathogens that leads to the initial antimicrobial regimens listed in Tables 1-3.

For many patients, monotherapy is adequate, but combination therapy is necessary in certain situations. These include episodes of HAP with a sufficiently broad spectrum of likely pathogens so that coverage by a single agent is impossible. Combination therapy may also be **necessary** if antimicrobial resistance is likely, if infection with *P. aeruginosa*, *Acinetobacter* spp., or other multiply resistant gram-negative organisms is probable, or if MRSA is suspected. After initiation of therapy, careful evaluation of clinical, physiologic, and microbiologic information is necessary to define whether the patient is having an appropriate response to therapy. Rapid deterioration or failure to improve **after 72 h** of empiric therapy necessitates a reevaluation and usually aggressive diagnostic testing. **Because** the diagnosis of HAP

is often imprecise, a nonresponse to empiric therapy may be the result of the presence of a noninfectious illness, or it may be the consequence of certain host and bacterial factors.

In the future, a number of unresolved questions will need to be examined. These will focus on the diagnosis of HAP, including the determinants of the specific pathogen(s), the duration of therapy, and the timing of switch to oral therapy. Ultimately, prevention of HAP is the most effective way to avoid **disease-associated mortality**. The available strategies and promising future approaches are reviewed in this document, and suggestions for the application of proven prevention approaches are presented.

This statement was prepared by an ad hoc Committee of the Scientific Assembly on Microbiology, Tuberculosis, and Pulmonary Infections. Members of the Committee were: C. Douglas Campbell, Jr., M.D. (Co-Chair); Michael S. Niederman, M.D. (Co-Chair); William A. Broughton, M.D.; Donald E. Craven, M.D.; Alan M. Fein, M.D.; Mitchell P. Fink, M.D.; Kevin Gleason, M.D.; Douglas B. Hornick, M.D.; Joseph P. Lynch, III, M.D.; Lionel A. Mandell, M.D.; Carol M. Mason, M.D.; Antoni Torres, M.D.; Richard C. Wunderink, M.D.

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