American Thoracic Society Documents

Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia

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EXECUTIVE SUMMARY

Since the initial 1996 American Thoracic Society (ATS) guideline on nosocomial pneumonia, a number of new developments have appeared, mandating a new evidence-based guideline for hospital-acquired pneumonia (HAP), including healthcare-associated pneumonia (HCAP) and ventilator-associated pneumonia (VAP). This document, prepared by a joint committee of the ATS and Infectious Diseases Society of America (IDSA), focuses on the epidemiology and pathogenesis of bacterial pneumonia in adults, and emphasizes modifiable risk factors for infection. In addition, the microbiology of HAP is reviewed, with an emphasis on multidrug-resistant (MDR) bacterial pathogens, such as *Pseudomonas aeruginosa*, *Acinetobacter* species, and methicillin-resistant *Staphylococcus aureus*. Controversies about diagnosis are discussed, emphasizing initial examination of lower respiratory tract samples for bacteria, and the rationale for both clinical and bacteriologic approaches, using either "semiquantitative" or "quantitative" microbiologic methods that help direct selection of appropriate antibiotic therapy. We also provide recommendations for additional diagnostic and therapeutic evaluations in patients with nonresolving pneumonia. This is an evidence-based document that emphasizes the issues of VAP, because there are far fewer data available about HAP in nonintubated patients and about HCAP. By extrapolation, patients who are not intubated and mechanically ventilated should be managed like patients with VAP, using the same approach to identify risk factors for infection with specific pathogens.

The major goals of this evidence-based guideline for the management of HAP, VAP, and HCAP emphasize early, appropriate antibiotics in adequate doses, while avoiding excessive antibiotics by de-escalation of initial antibiotic therapy, based on microbiologic cultures and the clinical response of the patient, and shortening the duration of therapy to the minimum effective period. The guideline recognizes the variability of bacteriology from one hospital to another and from one time period to another and recommends taking local microbiologic data into account when adapting treatment recommendations to any specific clinical setting. The initial, empiric antibiotic therapy algorithm includes two groups of patients: one with no need for broad-spectrum therapy, because these patients have early-onset HAP, VAP, or HCAP and no risk factors for MDR pathogens, and a second group that requires broad-spectrum therapy, because of late-onset pneumonia or other risk factors for infection with MDR pathogens.

Some of the key recommendations and principles in this new, evidence-based guideline are as follows:

- HCAP is included in the spectrum of HAP and VAP, and patients with HCAP need therapy for MDR pathogens.
- A lower respiratory tract culture needs to be collected from all patients before antibiotic therapy, but collection of cultures should not delay the initiation of therapy in critically ill patients.
- Either "semiquantitative" or "quantitative" culture data can be used for the management of patients with HAP.
- Lower respiratory tract cultures can be obtained broncho-

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scopically or nonbronchoscopically, and can be cultured quantitatively or semiquantitatively.
- Quantitative cultures increase specificity of the diagnosis of HAP without deleterious consequences, and the specific quantitative technique should be chosen on the basis of local expertise and experience.
- Negative lower respiratory tract cultures can be used to stop antibiotic therapy in a patient who has had cultures obtained in the absence of an antibiotic change in the past 72 hours.
- Early, appropriate, broad-spectrum, antibiotic therapy should be prescribed with adequate doses to optimize antimicrobial efficacy.
- An empiric therapy regimen should include agents that are from a different antibiotic class than the patient has recently received.
- Combination therapy for a specific pathogen should be used judiciously in the therapy of HAP, and consideration should be given to short-duration (5 days) aminoglycoside therapy, when used in combination with a β-lactam to treat *P. aeruginosa* pneumonia.
- Linezolid is an alternative to vancomycin, and unconfirmed, preliminary data suggest it may have an advantage for proven VAP due to methicillin-resistant *S. aureus*.
- Colistin should be considered as therapy for patients with VAP due to a carbapenem-resistant *Acinetobacter* species.
- Aerosolized antibiotics may have value as adjunctive therapy in patients with VAP due to some MDR pathogens.
- De-escalation of antibiotics should be considered once data are available on the results of lower respiratory tract cultures and the patient's clinical response.
- A shorter duration of antibiotic therapy (7 to 8 days) is recommended for patients with uncomplicated HAP, VAP, or HCAP who have received initially appropriate therapy and have had a good clinical response, with no evidence of infection with nonfermenting gram-negative bacilli.

INTRODUCTION

As with all guidelines, these new recommendations, although evidence graded, need validation for their impact on the outcome of patients with HAP, VAP, and HCAP. In addition, this guideline points out areas of incomplete knowledge, which can be used to set an agenda for future research.

Hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), and healthcare-associated pneumonia (HCAP) remain important causes of morbidity and mortality despite advances in antimicrobial therapy, better supportive care modalities, and the use of a wide-range of preventive measures (1–5). HAP is defined as pneumonia that occurs 48 hours or more after admission, which was not incubating at the time of admission (1, 3). HAP may be managed in a hospital ward or in the intensive care unit (ICU) when the illness is more severe. VAP refers to pneumonia that arises more than 48–72 hours after endotracheal intubation (2, 3). Although not included in this definition, some patients may require intubation after developing severe HAP and should be managed similar to patients with VAP. HCAP includes any patient who was hospitalized in an acute care hospital for two or more days within 90 days of the infection; resided in a nursing home or long-term care facility; received recent intravenous antibiotic therapy, chemotherapy, or wound care within the past 30 days of the current infection; or attended a hospital or hemodialysis clinic (3, 4, 6). Although this document focuses more on HAP and VAP, most of the principles overlap with HCAP. Because most of the current data have been collected from patients with VAP, and microbiologic data from nonintubated patients may be less accurate, most of our information is derived from those with VAP, but by extrapolation can be applied to all patients with HAP, emphasizing risk factors for infection with specific pathogens.

This guideline is an update of the 1996 consensus statement on HAP published by the American Thoracic Society (5). The principles and recommendations are largely based on data presented by committee members at a conference jointly sponsored by the American Thoracic Society (ATS) and the Infectious Disease Society of America (IDSA). The committee was composed of pulmonary, critical care, and infectious disease specialists with clinical and research interests in HAP, VAP, and HCAP. All major aspects of the epidemiology, pathogenesis, bacteriology, diagnosis, and antimicrobial treatment were reviewed by this group. Therapy recommendations are focused on antibiotic choice and patient stratification; adjunctive, nonantibiotic therapy of pneumonia is not discussed, but information on this topic is available elsewhere (7). Recommendations to reduce the risk of pneumonia are limited in this document to key, modifiable risk factors related to the pathogenesis of pneumonia to avoid redundancy with the more comprehensive Guidelines for Preventing Health-care–associated Pneumonia, prepared by the Centers for Disease Control and Prevention (CDC) and the Hospital Infection Control Practices Advisory Committee (HICPAC) (3).

The goal of our document is to provide a framework for the initial evaluation and management of the immunocompetent, adult patient with bacterial causes of HAP, VAP, or HCAP, and excludes patients who are known to be immunosuppressed by human immunodeficiency virus (HIV) infection, hematologic malignancy, chemotherapy-induced neutropenia, organ transplantation, and so on. At the outset, the ATS/IDSA Guideline Committee members recognized that currently, many patients with HAP, VAP, or HCAP are infected with multidrug-resistant (MDR) bacterial pathogens that threaten the adequacy of initial, empiric antibiotic therapy. At the same time, the committee members recognized that many studies have shown that excessive antibiotic use is a major factor contributing to increased frequency of antibiotic-resistant pathogens. Four major principles underlie the management of HAP, VAP, and HCAP:

- Avoid untreated or inadequately treated HAP, VAP, or HCAP, because the failure to initiate prompt appropriate and adequate therapy has been a consistent factor associated with increased mortality.
- Recognize the variability of bacteriology from one hospital to another, specific sites within the hospital, and from one time period to another, and use this information to alter the selection of an appropriate antibiotic treatment regimen for any specific clinical setting.
- Avoid the overuse of antibiotics by focusing on accurate diagnosis, tailoring therapy to the results of lower respiratory tract cultures, and shortening duration of therapy to the minimal effective period.
- Apply prevention strategies aimed at modifiable risk factors.

The ATS/IDSA guideline was established for use in the initial management of patients in whom HAP, VAP, or HCAP is suspected. Therapeutic algorithms are presented that are based on the expected antimicrobial susceptibility of the common bacterial pathogens, and with therapeutic regimens that can commonly lead to initial adequate antibiotic management.

This guideline is not meant to replace clinical judgment, but rather to give an organizational framework to patient management. Individual clinical situations can be highly complex and the judgment of a knowledgeable physician with all available information about a specific patient is essential for optimal clini-

TABLE 1. EVIDENCE-BASED GRADING SYSTEM USED TO RANK RECOMMENDATIONS

Evidence Level	Definition
Level I (high)	Evidence comes from well conducted, randomized controlled trials
Level II (moderate)	Evidence comes from well designed, controlled trials without randomization (including cohort, patient series, and case-control studies). Level II studies also include any large case series in which systematic analysis of disease patterns and/or microbial etiology was conducted, as well as reports of new therapies that were not collected in a randomized fashion
Level III (low)	Evidence comes from case studies and expert opinion. In some instances therapy recommendations come from antibiotic susceptibility data without clinical observations

Adapted from American Thoracic Society guidelines for the management of adults with community-acquired pneumonia (8).

cal management. As more laboratory and clinical data become available, therapy often needs to be streamlined or altered. Finally, our committee realizes that these guidelines will change over time, and that our current recommendations will need to be updated as new information becomes available.

METHODOLOGY USED TO PREPARE THE GUIDELINE

The ATS/IDSA Guideline Committee originally met as a group, with each individual being assigned a topic for review and presentation to the entire group. Each topic in the guideline was reviewed by more than one committee member, and after presentation of information, the committee discussed the data and formulated recommendations. Two committee members prepared each section of the document, and a draft document incorporating all sections was written and distributed to the committee for review and suggestions. The guideline was then revised and circulated to the committee for final comment. This final statement represents the results of this process and the opinions of the majority of committee members.

The grading system for our evidence-based recommendations was previously used for the updated ATS Community-acquired Pneumonia (CAP) statement, and the definitions of high-level (**Level I**), moderate-level (**Level II**), and low-level (**Level III**) evidence are summarized in Table 1 (8). All available and relevant, peer-reviewed studies published until July 2004 were considered. Much of the literature is observational, and only a few therapy trials have been conducted in a prospective, randomized fashion.

Nearly all of the evidence-based data on risk factors for bacterial HAP have been collected from observational studies, which cannot distinguish causation from noncausal association. Most of the studies have focused on patients with VAP, but the committee extrapolated the relationship between risk factors and bacteriology to all patients with HAP, including those with HCAP. Ultimate proof of causality, and ideally the best strategies for prevention of HAP, VAP, and HCAP, should be based on prospective, randomized trials. However, recommendations are further compromised when such trials provide conflicting results, often as a result of differences in definitions, study design, and the specific population studied. In addition, evidence-based recommendations are dynamic and may change as new therapies become available and as new interventions alter the natural history of the disease.

EPIDEMIOLOGY

Incidence

HAP is usually caused by bacteria, is currently the second most common nosocomial infection in the United States, and is associated with high mortality and morbidity (3). The presence of HAP increases hospital stay by an average of 7 to 9 days per patient and has been reported to produce an excess cost of more than $40,000 per patient (9–11). Although HAP is not a reportable illness, available data suggest that it occurs at a rate of between 5 and 10 cases per 1,000 hospital admissions, with the incidence increasing by as much as 6- to 20-fold in mechanically ventilated patients (9, 12, 13). It is often difficult to define the exact incidence of VAP, because there may be an overlap with other lower respiratory tract infections, such as infectious tracheobronchitis in mechanically ventilated patients. The exact incidence varies widely depending on the case definition of pneumonia and the population being evaluated (14). For example, the incidence of VAP may be up to two times higher in patients diagnosed by qualitative or semiquantitative sputum cultures compared with quantitative cultures of lower respiratory tract secretions (9, 15).

HAP accounts for up to 25% of all ICU infections and for more than 50% of the antibiotics prescribed (16). VAP occurs in 9–27% of all intubated patients (9, 11). In ICU patients, nearly 90% of episodes of HAP occur during mechanical ventilation. In mechanically ventilated patients, the incidence increases with duration of ventilation. The risk of VAP is highest early in the course of hospital stay, and is estimated to be 3%/day during the first 5 days of ventilation, 2%/day during Days 5 to 10 of ventilation, and 1%/day after this (17). Because most mechanical ventilation is short term, approximately half of all episodes of VAP occur within the first 4 days of mechanical ventilation. The intubation process itself contributes to the risk of infection, and when patients with acute respiratory failure are managed with noninvasive ventilation, nosocomial pneumonia is less common (18–20).

Time of onset of pneumonia is an important epidemiologic variable and risk factor for specific pathogens and outcomes in patients with HAP and VAP. Early-onset HAP and VAP, defined as occurring within the first 4 days of hospitalization, usually carry a better prognosis, and are more likely to be caused by antibiotic-sensitive bacteria. Late-onset HAP and VAP (5 days or more) are more likely to be caused by multidrug-resistant (MDR) pathogens, and are associated with increased patient mortality and morbidity. However, patients with early-onset HAP who have received prior antibiotics or who have had prior hospitalization within the past 90 days are at greater risk for colonization and infection with MDR pathogens and should be treated similar to patients with late-onset HAP or VAP (Table 2) (21).

The crude mortality rate for HAP may be as high as 30 to 70%, but many of these critically ill patients with HAP die of their underlying disease rather than pneumonia. The mortality related to the HAP or "attributable mortality" has been estimated to be between 33 and 50% in several case-matching studies of VAP. Increased mortality rates were associated with bacteremia, especially with *Pseudomonas aeruginosa* or *Acinetobacter* species, medical rather than surgical illness, and treatment with ineffective antibiotic therapy (22, 23). Other studies using similar methodology failed to identify any attributable mortality due to VAP,

TABLE 2. RISK FACTORS FOR MULTIDRUG-RESISTANT PATHOGENS CAUSING HOSPITAL-ACQUIRED PNEUMONIA, HEALTHCARE-ASSOCIATED PNEUMONIA, AND VENTILATOR-ASSOCIATED PNEUMONIA

- Antimicrobial therapy in preceding 90 d
- Current hospitalization of 5 d or more
- High frequency of antibiotic resistance in the community or in the specific hospital unit
- Presence of risk factors for HCAP:
  - Hospitalization for 2 d or more in the preceding 90 d
  - Residence in a nursing home or extended care facility
  - Home infusion therapy (including antibiotics)
  - Chronic dialysis within 30 d
  - Home wound care
  - Family member with multidrug-resistant pathogen
- Immunosuppressive disease and/or therapy

suggesting a variable outcome impact, according to the severity of underlying medical conditions (24–26).

Etiology

HAP, VAP, and HCAP may be caused by a wide spectrum of bacterial pathogens, may be polymicrobial, and are rarely due to viral or fungal pathogens in immunocompetent hosts (9, 12, 27–32). Common pathogens include aerobic gram-negative bacilli, such as *P. aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Acinetobacter* species. Infections due to gram-positive cocci, such as *Staphylococcus aureus*, particularly methicillin-resistant *S. aureus* (MRSA), have been rapidly emerging in the United States (16, 33). Pneumonia due to *S. aureus* is more common in patients with diabetes mellitus, head trauma, and those hospitalized in ICUs (34).

Significant growth of oropharyngeal commensals (viridans group streptococci, coagulase-negative staphylococci, *Neisseria* species, and *Corynebacterium* species) from distal bronchial specimens is difficult to interpret, but these organisms can produce infection in immunocompromised hosts and some immunocompetent patients (35). Rates of polymicrobial infection vary widely, but appear to be increasing, and are especially high in patients with adult respiratory distress syndrome (ARDS) (9, 12, 36–38).

The frequency of specific MDR pathogens causing HAP may vary by hospital, patient population, exposure to antibiotics, type of ICU patient, and changes over time, emphasizing the need for timely, local surveillance data (3, 8, 10, 21, 39–41). HAP involving anaerobic organisms may follow aspiration in nonintubated patients, but is rare in patients with VAP (28, 42).

Elderly patients represent a diverse population of patients with pneumonia, particularly HCAP. Elderly residents of long-term care facilities have been found to have a spectrum of pathogens that more closely resemble late-onset HAP and VAP (30, 31). In a study of 104 patients age 75 years and older with severe pneumonia, El-Solh found *S. aureus* (29%), enteric gram-negative rods (15%), *Streptococcus pneumoniae* (9%), and *Pseudomonas* species (4%) as the most frequent causes of nursing home-acquired pneumonia (30). In another study of 52 long-term care residents aged 70 years and above who failed to respond to 72 hours of antibiotics, MRSA (33%), gram-negative enterics (24%), and *Pseudomonas* species (14%) were the most frequent pathogens isolated by invasive diagnostics (bronchoscopy) (31). In the latter study, 72% had at least two comorbidities whereas 23% had three or more.

Few data are available about the bacteriology and risk factors for specific pathogens in patients with HAP and HCAP, and who are not mechanically ventilated. Data from comprehensive hospital-wide surveillance of nosocomial infections at the University of North Carolina have described the pathogens causing both VAP and nosocomial pneumonia in nonintubated patients during the years 2000–2003 (D. Weber and W. Rutala, unpublished data). Pathogens were isolated from 92% of mechanically ventilated patients with infection, and from 77% of nonventilated patients with infection. In general, the bacteriology of nonventilated patients was similar to that of ventilated patients, including infection with MDR pathogens such as methicillin-resistant *S. aureus* (MRSA), *P. aeruginosa*, *Acinetobacter* species, and *K. pneumoniae*. In fact, some organisms (MRSA and *K. pneumoniae*) were more common in nonventilated than ventilated patients, whereas certain resistant gram-negative bacilli were more common in patients with VAP (*P. aeruginosa, Stenotrophomonas maltophilia*, and *Acinetobacter* species). However, the latter group of more resistant gram-negative bacilli occurred with sufficient frequency in nonventilated patients that they should be considered when designing an empiric therapy regimen. Studies in nonventilated patients have not determined whether this population has risk factors for MDR pathogens that differ from the risk factors present in ventilated patients.

Emergence of selected multidrug-resistant bacteria. Rates of HAP due to MDR pathogens have increased dramatically in hospitalized patients, especially in intensive care and transplant patients (16). Risk factors for colonization and infection with MDR pathogens are summarized in Table 2 (21, 43). Data on mechanisms of antibiotic resistance for specific bacterial pathogens have provided new insight into the adaptability of these pathogens.

Pseudomonas aeruginosa. *P. aeruginosa*, the most common MDR gram-negative bacterial pathogen causing HAP/VAP, has intrinsic resistance to many antimicrobial agents (44–46). This resistance is mediated by multiple efflux pumps, which may be expressed all the time or may be upregulated by mutation (47). Resistance to piperacillin, ceftazidime, cefepime, other oxyimino-β-lactams, imipenem and meropenem, aminoglycosides, or fluoroquinolones is increasing in the United States (16). Decreased expression of an outer membrane porin channel (OprD) can cause resistance to both imipenem and meropenem or, depending on the alteration in OprD, specific resistance to imipenem, but not other β-lactams (48). At present, some MDR isolates of *P. aeruginosa* are susceptible only to polymyxin B.

Although currently uncommon in the United States, there is concern about the acquisition of plasmid-mediated metallo-β-lactamases active against carbapenems and antipseudomonal penicillins and cephalosporins (49). The first such enzyme, IMP-1, appeared in Japan in 1991 and spread among *P. aeruginosa* and *Serratia marcescens*, and then to other gram-negative pathogens. Resistant strains of *P. aeruginosa* with IMP-type enzymes and other carbapenemases have been reported from additional countries in the Far East, Europe, Canada, Brazil, and recently in the United States (50).

Klebsiella, Enterobacter, and Serratia species. *Klebsiella* species are intrinsically resistant to ampicillin and other aminopenicillins and can acquire resistance to cephalosporins and aztreonam by the production of extended-spectrum β-lactamases (ESBLs) (51). Plasmids encoding ESBLs often carry resistance to aminoglycosides and other drugs, but ESBL-producing strains remain susceptible to carbapenems. Five to 10% of oxyimino-β-lactam-resistant *K. pneumoniae* do not produce an ESBL, but rather a plasmid-mediated AmpC-type enzyme (52). Such strains usually are carbapenem susceptible, but may become resistant by loss of an outer membrane porin (53). *Enterobacter* species have a chromosomal AmpC β-lactamase that is inducible and also easily expressed at a high level by mutation with consequent resistance to oxyimino-β-lactams and α-methoxy-β-lactams,

such as cefoxitin and cefotetan, but continued susceptibility to carbapenems. *Citrobacter* and *Serratia* species have the same inducible AmpC β-lactamase and the same potential for resistance development. Although the AmpC enzyme of *E. coli* is not inducible, it can occasionally be hyperexpressed. Plasmid-mediated resistance, such as ESBL production, is a more common mechanism for β-lactam resistance in nosocomial isolates, and is increasingly recognized not only in isolates of *K. pneumoniae* and *E. coli*, but also *Enterobacter* species (54).

Acinetobacter species, *Stenotrophomonas maltophilia*, and *Burkholderia cepacia*. Although generally less virulent than *P. aeruginosa, Acinetobacter* species have nonetheless become problem pathogens because of increasing resistance to commonly used antimicrobial agents (55). More than 85% of isolates are susceptible to carbapenems, but resistance is increasing due either to IMP-type metalloenzymes or carbapenemases of the OXA type (49). An alternative for therapy is sulbactam, usually employed as an enzyme inhibitor, but with direct antibacterial activity against *Acinetobacter* species (56). *S. maltophilia*, which shares with *B. cepacia* a tendency to colonize the respiratory tract rather than cause invasive disease, is uniformly resistant to carbapenems, because of a ubiquitous metallo-β-lactamase. *S. maltophilia* and *B. cepacia* are most likely to be susceptible to trimethoprim–sulfamethoxazole, ticarcillin–clavulanate, or a fluoroquinolone (55). *B. cepacia* is also usually susceptible to ceftazidime and carbapenems.

Methicillin-resistant *Staphylococcus aureus*. In the United States, more than 50% of the ICU infections caused by *S. aureus* are with methicillin-resistant organisms (16, 33). MRSA produces a penicillin-binding protein with reduced affinity for β-lactam antibiotics that is encoded by the *mecA* gene, which is carried by one of a family of four mobile genetic elements (57, 58). Strains with *mecA* are resistant to all commercially available β-lactams and many other antistaphylococcal drugs, with considerable country-to-country variability (59, 60). Although vancomycin-intermediate *S. aureus*, with a minimal inhibitory concentration (MIC) of 8–16 μg/ml, and high-level vancomycin-resistant *S. aureus*, with an MIC of 32–1,024 μg/ml or more, have been isolated from clinical specimens, none to date have caused respiratory tract infection and all have been sensitive to linezolid (61, 62). Unfortunately, linezolid resistance has emerged in *S. aureus*, but is currently rare (63).

Streptococcus pneumoniae and *Haemophilus influenzae*. *S. pneumoniae* and *H. influenzae* cause early-onset HAP in patients without other risk factors, are uncommon in late-onset infection, and frequently are community acquired. At present, many strains of *S. pneumoniae* are penicillin resistant due to altered penicillin-binding proteins. Some such strains are resistant as well to cephalosporins, macrolides, tetracyclines, and clindamycin (64). Despite low and moderate levels of resistance to penicillins and cephalosporins *in vitro*, clinical outcomes in patients with pneumococcal pneumonia and bacteremia treated with these agents have been satisfactory (65). All of the multidrug-resistant strains in the United States are currently sensitive to vancomycin or linezolid, and most remain sensitive to broad-spectrum quinolones. Resistance of *H. influenzae* to antibiotics other than penicillin and ampicillin is sufficiently rare so as not to present a problem in therapy.

Legionella pneumophila. The evidence for *Legionella pneumophila* as a cause of HAP is variable, but is increased in immunocompromised patients, such as organ transplant recipients or patients with HIV disease, as well as those with diabetes mellitus, underlying lung disease, or end-stage renal disease (29, 66–69). HAP due to *Legionella* species is more common in hospitals where the organism is present in the hospital water supply or where there is ongoing construction (3, 29, 66–69). Because detection is based on the widespread use of *Legionella* urinary antigen, rather than culture for *Legionella*, disease due to serogroups other than serogroup 1 may be underdiagnosed. Detailed strategies for prevention of *Legionella* infections and eradication procedures for *Legionella* species in cooling towers and the hospital water supply are outlined in the CDC/HICPAC Guidelines for Preventing Health-care–associated Pneumonia (3).

Fungal pathogens. Nosocomial pneumonia due to fungi, such as *Candida* species and *Aspergillus fumigatus*, may occur in organ transplant or immunocompromised, neutropenic patients, but is uncommon in immunocompetent patients (70–75). Nosocomial *Aspergillus* species infections suggest possible airborne transmission by spores, and may be associated with an environmental source such as contaminated air ducts or hospital construction. By comparison, isolation of *Candida albicans* and other *Candida* species from endotracheal aspirates is common, but usually represents colonization of the airways, rather than pneumonia in immunocompetent patients, and rarely requires treatment with antifungal therapy (70).

Viral pathogens. The incidence of HAP and VAP due to viruses is also low in immunocompetent hosts. Outbreaks of HAP, VAP, and HCAP due to viruses, such as influenza, parainfluenza, adenovirus, measles, and respiratory syncytial virus have been reported and are usually seasonal. Influenza, pararinfluenza, adenovirus, and respiratory syncytial virus account for 70% of the nosocomial viral cases of HAP, VAP, and HCAP (3, 76–78). Respiratory syncytial virus outbreaks of bronchiolitis and pneumonia are more common in children's wards and rare in immunocompetent adults (76). Diagnosis of these viral infections is often made by rapid antigen testing and viral culture or serologic assays.

Influenza A is probably the most common viral cause of HAP and HCAP in adult patients. Pneumonia in patients with influenza A or B may be due to the virus, to secondary bacterial infection, or both. Influenza is transmitted directly from person to person when infected persons sneeze, cough, or talk or indirectly by person–fomite–person transmission (3, 79–81). The use of influenza vaccine along with prophylaxis and early antiviral therapy among at-risk healthcare workers and high-risk patients with amantadine, rimantadine, or one of the neuraminidase inhibitors (oseltamivir and zanamivir) dramatically reduces the spread of influenza within hospital and healthcare facilities (3, 81–90). Amantadine and rimantadine are effective only for treatment and prophylaxis against influenza A strains, whereas neuraminidase inhibitors are effective against both influenza A and B.

Major Epidemiologic Points

1. Many patients with HAP, VAP, and HCAP are at increased risk for colonization and infection with MDR pathogens (**Level II**) (2–4, 6, 9, 11–13, 21, 22).
2. It is often difficult to define the exact incidence of HAP and VAP, because there may be an overlap with other lower respiratory tract infections, such as tracheobronchitis, especially in mechanically ventilated patients (**Level III**) (9, 12–14).
3. The exact incidence of HAP is usually between 5 and 15 cases per 1,000 hospital admissions depending on the case definition and study population; the exact incidence of VAP is 6- to 20-fold greater than in nonventilated patients (**Level II**) (9, 12–14).
4. HAP and VAP are a frequent cause of nosocomial infection that is associated with a higher crude mortality than other hospital-acquired infections (**Level II**) (3, 9, 16).
5. Patients with late-onset HAP and VAP are more likely to be infected with MDR pathogens and have higher

crude mortality than patients with early-onset disease; patients with early-onset HAP who have recently received antibiotics or had an admission to a healthcare facility are at risk for colonization and infection with MDR pathogens (**Level II**) (3, 9, 21, 22).

6. An increase in crude and attributable mortality for HAP and VAP is associated with the presence of MDR pathogens (**Level II**) (3, 5, 9–13, 21–23).
7. Bacteria cause most cases of HAP, VAP, and HCAP and many infections are polymicrobial; rates are especially high in patients with ARDS (**Level I**) (2, 4, 6, 9, 12, 36–38).
8. HAP, VAP, and HCAP are commonly caused by aerobic gram-negative bacilli, such as *P. aeruginosa, K. pneumoniae*, and *Acinetobacter* species, or by gram-positive cocci, such as *S. aureus*, much of which is MRSA; anaerobes are an uncommon cause of VAP (**Level II**) (9, 12, 28, 36–40, 42, 91).
9. Rates of *L. pneumophila* vary considerably between hospitals and disease occurs more commonly with serogroup 1 when the water supply is colonized or there is ongoing construction (**Level II**) (29, 66–69).
10. Nosocomial virus and fungal infections are uncommon causes of HAP and VAP in immunocompetent patients. Outbreaks of influenza have occurred sporadically and risk of infection can be substantially reduced with widespread effective infection control, vaccination, and use of antiinfluenza agents (**Level I**) (3, 70–75, 79–90).
11. The prevalence of MDR pathogens varies by patient population, hospital, and type of ICU, which underscores the need for local surveillance data (**Level II**) (3, 9, 41).
12. MDR pathogens are more commonly isolated from patients with severe, chronic underlying disease, those with risk factors for HCAP, and patients with late-onset HAP or VAP (**Level II**) (9, 21, 22, 30, 31, 39, 40, 91).

PATHOGENESIS

For HAP to occur, the delicate balance between host defenses and microbial propensity for colonization and invasion must shift in favor of the ability of the pathogens to persist and invade the lower respiratory tract. Sources of infection for HAP include healthcare devices or the environment (air, water, equipment, and fomites) and can occur with transfer of microorganisms between staff and patients (3, 9, 12, 13, 27, 66, 92, 93). A number of host- and treatment-related colonization factors, such as the severity of the patient's underlying disease, prior surgery, exposure to antibiotics, other medications, and exposure to invasive respiratory devices and equipment, are important in the pathogenesis of HAP and VAP (40, 93, 94)

HAP requires the entry of microbial pathogens into the lower respiratory tract, followed by colonization, which can then overwhelm the host's mechanical (ciliated epithelium and mucus), humoral (antibody and complement), and cellular (polymorphonuclear leukocytes, macrophages, and lymphocytes and their respective cytokines) defenses to establish infection (9, 94).

Aspiration of oropharyngeal pathogens or leakage of bacteria around the endotracheal tube cuff is the primary route of bacterial entry into the trachea (95–98). The stomach and sinuses have been suggested as potential reservoirs for certain bacteria colonizing the oropharynx and trachea, but their importance remains controversial (99–104). Some investigators postulate that colonization of the endotracheal tube with bacteria encased in biofilm may result in embolization into the alveoli during suctioning or bronchoscopy (105, 106). Inhalation of pathogens from contaminated aerosols, and direct inoculation, are less common (107, 108). Hematogenous spread from infected intravascular catheters or bacterial translocation from the gastrointestinal tract lumen are quite rare.

Major Points for Pathogenesis

1. Sources of pathogens for HAP include healthcare devices, the environment (air, water, equipment, and fomites), and commonly the transfer of microorganisms between the patient and staff or other patients (**Level II**) (3, 9, 12, 13, 27, 66, 92, 93).
2. A number of host- and treatment-related colonization factors, such as the severity of the patient's underlying disease, prior surgery, exposure to antibiotics, other medications, and exposure to invasive respiratory devices and equipment, are important in the pathogenesis of HAP and VAP (**Level II**) (40, 93, 94).
3. Aspiration of oropharyngeal pathogens, or leakage of secretions containing bacteria around the endotracheal tube cuff, are the primary routes of bacterial entry into the lower respiratory tract (**Level II**) (95–98).
4. Inhalation or direct inoculation of pathogens into the lower airway, hematogenous spread from infected intravenous catheters, and bacterial translocation from the gastrointestinal tract lumen are uncommon pathogenic mechanisms (**Level II**) (107, 108).
5. Infected biofilm in the endotracheal tube, with subsequent embolization to distal airways, may be important in the pathogenesis of VAP (**Level III**) (105, 106).
6. The stomach and sinuses may be potential reservoirs of nosocomial pathogens that contribute to bacterial colonization of the oropharynx, but their contribution is controversial, may vary by the population at risk, and may be decreasing with the changing natural history and management of HAP (**Level II**) (94, 99–104, 109).

MODIFIABLE RISK FACTORS

Risk factors for the development of HAP can be differentiated into modifiable and nonmodifiable conditions. Risk factors may also be patient related (male sex, preexisting pulmonary disease, or multiple organ system failure) or treatment related (intubation or enteral feeding). Modifiable risk factors for HAP are obvious targets for improved management and prophylaxis in several studies and in the comprehensive Guidelines for Preventing Health-care–associated Pneumonia, published by the Centers for Disease Control (3, 93, 110). Effective strategies include strict infection control, alcohol-based hand disinfection, use of microbiologic surveillance with timely availability of data on local MDR pathogens, monitoring and early removal of invasive devices, and programs to reduce or alter antibiotic-prescribing practices (3, 92, 93, 100, 110–113).

Intubation and Mechanical Ventilation

Intubation and mechanical ventilation increase the risk of HAP 6- to 21-fold and therefore should be avoided whenever possible (3, 94, 110, 114). Noninvasive positive-pressure ventilation, using a face mask, is an attractive alternative for patients with acute exacerbations of chronic obstructive pulmonary disease or acute hypoxemic respiratory failure, and for some immunosuppressed patients with pulmonary infiltrates and respiratory failure (18, 20, 115–119). Data suggest that use of noninvasive ventilation to avoid reintubation after initial extubation may not be a good strategy (115).

Specific strategies have been recommended to reduce the duration of mechanical ventilation, such as improved methods

of sedation and the use of protocols to facilitate and accelerate weaning (120–124). These interventions are dependent on adequate ICU staffing. Reintubation should be avoided, if possible, as it increases the risk of VAP (114).

Attention to the specific type of endotracheal tube, its maintenance, and the site of insertion may also be valuable. The use of oral endotracheal and orogastric tubes, rather than nasotracheal and nasogastric tubes, can reduce the frequency of nosocomial sinusitis and possibly HAP, although causality between sinusitis and HAP has not been firmly established (109, 125). Efforts to reduce the likelihood of aspiration of oropharyngeal bacteria around the endotracheal tube cuff and into the lower respiratory tract include limiting the use of sedative and paralytic agents that depress cough and other host-protective mechanisms, and maintaining endotracheal cuff pressure at greater than 20 cm H_2O (98, 126). Continuous aspiration of subglottic secretions, through the use of a specially designed endotracheal tube, has significantly reduced the incidence of early-onset VAP in several studies (97, 127–130).

VAP may also be related to colonization of the ventilator circuit (131). A large number of prospective, randomized trials have shown that the frequency of ventilator circuit change does not affect the incidence of HAP, but condensate collecting in the ventilator circuit can become contaminated from patient secretions (98, 132–135). Therefore, vigilance is needed to prevent inadvertently flushing the condensate into the lower airway or to in-line medication nebulizers when the patient turns or the bedrail is raised (98, 131–134, 136). Passive humidifiers or heat–moisture exchangers decrease ventilator circuit colonization but have not significantly reduced the incidence of VAP (128, 135–139).

Aspiration, Body Position, and Enteral Feeding

Supine patient positioning may also facilitate aspiration, which may be decreased by a semirecumbent positioning (140–142). Using radioactive labeled enteral feeding, cumulative numbers of endotracheal counts were higher when patients were placed in the completely supine position (0°) as compared with a semirecumbent position (45°) (140, 141). One randomized trial demonstrated a threefold reduction in the incidence of ICU-acquired HAP in patients treated in the semirecumbent position compared with patients treated completely supine (143). Infection in patients in the supine position was strongly associated with the simultaneous administration of enteral nutrition. Thus, intubated patients should be managed in a semirecumbent position, particularly during feeding.

Enteral nutrition has been considered a risk factor for the development of HAP, mainly because of an increased risk of aspiration of gastric contents (3, 144). However, its alternative, parenteral nutrition, is associated with higher risks for intravascular device-associated infections, complications of line insertions, higher costs, and loss of intestinal villous architecture, which may facilitate enteral microbial translocation. Although some have advised feeding critically ill patients enterally as early as possible, a strategy of early (i.e., Day 1 of intubation and ventilation) enteral feeding was, when compared with late administration (i.e., Day 5 of intubation), associated with a higher risk for ICU-acquired VAP (145, 146). Seven studies have evaluated the risks for ICU-acquired HAP in patients randomized to either gastric or postpyloric feeding (147). Although significant differences were not demonstrated in any individual study, postpyloric feeding was associated with a significant reduction in ICU-acquired HAP in metaanalysis (relative risk, 0.76; 95% confidence interval, 0.59 to 0.99) (147).

Modulation of Colonization: Oral Antiseptics and Antibiotics

The progression from colonization to tracheobronchitis to pneumonia is a dynamic equilibrium and the possibility to discern the different entities depends on the specificity of diagnostic tools. Oropharyngeal colonization, either present on admission or acquired during ICU stay, has been identified as an independent risk factor for the development of ICU-acquired HAP caused by enteric gram-negative bacteria and *P. aeruginosa* (101). In a randomized trial, DeRiso and coworkers demonstrated that the use of the oral antiseptic chlorhexidine significantly reduced rates of nosocomial infection in patients undergoing coronary artery bypass surgery (148).

Modulation of oropharyngeal colonization, by combinations of oral antibiotics, with or without systemic therapy, or by selective decontamination of the digestive tract (SDD), is also effective in significantly reducing the frequency of HAP, although methodologic study quality appeared to be inversely related to the magnitude of the preventive effects (93, 149–155).

In two prospective randomized trials SDD was associated with higher ICU survival among patients receiving SDD (156, 157). In the first study patients with a midrange APACHE II score on admission had a lower ICU mortality, although ICU mortality rates of all patients included did not differ significantly (156). In the largest study performed so far, SDD administered to 466 patients in one unit was associated with a relative risk for ICU mortality of 0.65 and with a relative risk of hospital mortality of 0.78, when compared with 472 patients admitted in a control ward (157). In addition, infections due to antibiotic-resistant microorganisms occurred more frequently in the control ward. Importantly, levels of antibiotic-resistant pathogens were low in both wards, with complete absence of MRSA. Moreover, a small preexisting difference in outcome between two wards and the absence of a cross-over design warrant confirmation of these beneficial effects of SDD.

The preventive effects of selective decontamination of the digestive tract for HAP have also been considerably lower in ICUs with high endemic levels of antibiotic resistance. In such a setting, selective decontamination of the digestive tract may increase the selective pressure for antibiotic-resistant microorganisms (158–164). Although selective decontamination of the digestive tract reduces HAP, routine prophylactic use of antibiotics should be discouraged, especially in hospital settings where there are high levels of antibiotic resistance.

The role of systemic antibiotics in the development of HAP is less clear. In one study, prior administration of antibiotics had an adjusted odds ratio of 3.1 (95% confidence interval, 1.4–6.9) for development of late-onset ICU-acquired HAP (165). Moreover, antibiotics clearly predispose patients to subsequent colonization and infection with antibiotic-resistant pathogens (21). In contrast, prior antibiotic exposure conferred protection (risk ratio, 0.37; 95% confidence interval, 0.27–0.51) for ICU-acquired HAP in another study (17). In addition, antibiotic use at the time of emergent intubation may prevent pneumonia within the first 48 hours of intubation (166). Preventive effects of intravenous antibiotics were evaluated in only one randomized trial: administration of cefuroxime for 24 hours, at the time of intubation; and it reduced the incidence of early-onset, ICU-acquired HAP in patients with closed head injury (167). However, circumstantial evidence of the efficacy of systemic antibiotics also follows from the results of metaanalyses of selective decontamination of the digestive tract, which have suggested that the intravenous component of the regimens was largely responsible for improved survival (149). In summary, prior administration of antibiotics for short duration may be beneficial in some patient groups, but when

given for prolonged periods may well place others at risk for subsequent infection with antibiotic-resistant microorganisms.

Stress Bleeding Prophylaxis, Transfusion, and Glucose Control

Both histamine Type 2 (H_2) antagonists and antacids have been identified as independent risk factors for ICU-acquired HAP. Sucralfate has been used for stress bleeding prophylaxis, as it does not decrease intragastric acidity or significantly increase gastric volume. Numerous randomized trials, using different doses and various study populations, have provided controversial results on the benefits of specific stress bleeding prophylaxis agents in relation to the increased risk of VAP (38, 99, 103, 104, 155, 168). One large randomized trial comparing antacids, H_2 blockers, and sucralfate reported no differences in rates of early-onset VAP, but rates of late-onset VAP were lower among patients treated with sucralfate (103). In one multicenter study of VAP in patients with ARDS, sucralfate and duration of exposure to sucralfate were associated with an increased risk of VAP (38). A large, double-blind, randomized trial comparing ranitidine with sucralfate demonstrated a trend to toward lower rates of VAP with sucralfate, but clinically significant gastrointestinal bleeding was 4% higher in the sucralfate group (104). Thus, if stress ulcer prophylaxis is indicated, the risks and benefits of each regimen should be weighed before prescribing either H_2 blockers or sucralfate.

A landmark prospective randomized trial comparing liberal and conservative "triggers" to transfusion in ICU patients not exhibiting active bleeding and without underlying cardiac disease demonstrated that awaiting a hemoglobin level of 7.0 g/dl as opposed to a level of 9.0 g/dl before initiating transfusion resulted in less transfusion and no adverse effects on outcome (169). In fact, in those patients less severely ill, as judged by low APACHE II scores, mortality was improved in the "restricted transfusion" group, a result thought to result from immunosuppressive effects of non–leukocyte-depleted red blood cell units with consequent increased risk for infection. Multiple studies have identified exposure to allogeneic blood products as a risk factor for postoperative infection and postoperative pneumonia, and the length of time of blood storage as another factor modulating risk (170–174). In one prospective randomized control trial the use of leukocyte-depleted red blood cell transfusions resulted in a reduced incidence of postoperative infections, and specifically a reduced incidence of pneumonia in patients undergoing colorectal surgery (172). Routine red blood cell transfusion should be conducted with a restricted transfusion trigger policy. Whether leukocyte-depleted red blood cell transfusions will further reduce the incidence of pneumonia in broad populations of patients at risk remains to be determined.

Hyperglycemia, relative insulin deficiency, or both may directly or indirectly increase the risk of complications and poor outcomes in critically ill patients. van den Berghe and coworkers randomized surgical intensive care unit patients to receive either intensive insulin therapy to maintain blood glucose levels between 80 and 110 mg/dl or to receive conventional treatment (175). The group receiving intensive insulin therapy had reduced mortality (4.6 versus 8%, $p < 0.04$) and the difference was greater in patients who remained in the intensive care unit more than 5 days (10.6 versus 20.2%, $p = 0.005$). When compared with the control group, those treated with intensive insulin therapy had a 46% reduction of bloodstream infections, decreased frequency of acute renal failure requiring dialysis by 41%, fewer antibiotic treatment days, and significantly shorter length of mechanical ventilation and ICU stay. Although the same degree of benefit may not be seen among patients with VAP as in other populations, aggressive treatment of hyperglycemia has both theoretical and clinical support.

Major Points and Recommendations for Modifiable Risk Factors

General prophylaxis.

1. Effective infection control measures: staff education, compliance with alcohol-based hand disinfection, and isolation to reduce cross-infection with MDR pathogens should be used routinely (**Level I**) (3, 93, 100, 110, 111).
2. Surveillance of ICU infections, to identify and quantify endemic and new MDR pathogens, and preparation of timely data for infection control and to guide appropriate, antimicrobial therapy in patients with suspected HAP or other nosocomial infections, are recommended (**Level II**) (3, 92, 93, 100, 110–113).

Intubation and mechanical ventilation.

1. Intubation and reintubation should be avoided, if possible, as it increases the risk of VAP (**Level I**) (3, 12, 93, 94, 114).
2. Noninvasive ventilation should be used whenever possible in selected patients with respiratory failure (**Level I**) (18, 20, 115–119).
3. Orotracheal intubation and orogastric tubes are preferred over nasotracheal intubation and nasogastric tubes to prevent nosocomial sinusitis and to reduce the risk of VAP, although direct causality has not been proved (**Level II**) (3, 93, 94, 109, 125).
4. Continuous aspiration of subglottic secretions can reduce the risk of early-onset VAP, and should be used, if available (**Level I**) (97, 128, 130).
5. The endotracheal tube cuff pressure should be maintained at greater than 20 cm H_2O to prevent leakage of bacterial pathogens around the cuff into the lower respiratory tract (**Level II**) (98, 126).
6. Contaminated condensate should be carefully emptied from ventilator circuits and condensate should be prevented from entering either the endotracheal tube or in-line medication nebulizers (**Level II**) (98, 131, 132).
7. Passive humidifiers or heat–moisture exchangers decrease ventilator circuit colonization, but have not consistently reduced the incidence of VAP, and thus they cannot be regarded as a pneumonia prevention tool (**Level I**) (135–139).
8. Reduced duration of intubation and mechanical ventilation may prevent VAP and can be achieved by protocols to improve the use of sedation and to accelerate weaning (**Level II**) (93, 120–122, 124).
9. Maintaining adequate staffing levels in the ICU can reduce length of stay, improve infection control practices, and reduce duration of mechanical ventilation (**Level II**) (121–124).

Aspiration, body position, and enteral feeding.

1. Patients should be kept in the semirecumbent position (30–45°) rather than supine to prevent aspiration, especially when receiving enteral feeding (**Level I**) (140–144).
2. Enteral nutrition is preferred over parenteral nutrition to reduce the risk of complications related to central intravenous catheters and to prevent reflux villous atrophy of the intestinal mucosa that may increase the risk of bacterial translocation (**Level I**) (3, 93, 145, 146).

Modulation of colonization: oral antiseptics and antibiotics.

1. Routine prophylaxis of HAP with oral antibiotics (selective decontamination of the digestive tract or SDD), with or without systemic antibiotics, reduces the incidence of ICU-acquired VAP, has helped contain outbreaks of

MDR bacteria (**Level I**), but is not recommended for routine use, especially in patients who may be colonized with MDR pathogens (**Level II**) (149–154, 156–159, 161–164, 176).

2. Prior administration of systemic antibiotics has reduced the risk of nosocomial pneumonia in some patient groups, but if a history of prior administration is present at the time of onset of infection, there should be increased suspicion of infection with MDR pathogens (**Level II**) (157–159, 161–164).
3. Prophylactic administration of systemic antibiotics for 24 hours at the time of emergent intubation has been demonstrated to prevent ICU-acquired HAP in patients with closed head injury in one study, but its routine use is not recommended until more data become available (**Level I**) (167).
4. Modulation of oropharyngeal colonization by the use of oral chlorhexidine has prevented ICU-acquired HAP in selected patient populations such as those undergoing coronary bypass grafting, but its routine use is not recommended until more data become available (**Level I**) (148).
5. Use daily interruption or lightening of sedation to avoid constant heavy sedation and try to avoid paralytic agents, both of which can depress cough and thereby increase the risk of HAP (**Level II**) (120).

Stress bleeding prophylaxis, transfusion, and hyperglycemia.

1. Comparative data from randomized trials suggest a trend toward reduced VAP with sucralfate, but there is a slightly higher rate of clinically significant gastric bleeding, compared with H_2 antagonists. If needed, stress bleeding prophylaxis with either H_2 antagonists or sucralfate is acceptable (**Level I**) (99–104, 155, 177–179).
2. Transfusion of red blood cell and other allogeneic blood products should follow a restricted transfusion trigger policy; leukocyte-depleted red blood cell transfusions can help to reduce HAP in selected patient populations (**Level I**) (169–174).
3. Intensive insulin therapy is recommended to maintain serum glucose levels between 80 and 110 mg/dl in ICU patients to reduce nosocomial blood stream infections, duration of mechanical ventilation, ICU stay, morbidity, and mortality (**Level I**) (175).

DIAGNOSTIC TESTING

Diagnostic testing is ordered for two purposes: to define whether a patient has pneumonia as the explanation for a constellation of new signs and symptoms and to determine the etiologic pathogen when pneumonia is present. Unfortunately, currently available tools cannot always reliably provide this information.

The diagnosis of HAP is suspected if the patient has a radiographic infiltrate that is new or progressive, along with clinical findings suggesting infection, which include the new onset of fever, purulent sputum, leukocytosis, and decline in oxygenation. When fever, leukocytosis, purulent sputum, and a positive culture of a sputum or tracheal aspirate are present without a new lung infiltrate, the diagnosis of nosocomial tracheobronchitis should be considered (180). When this definition has been applied to mechanically ventilated patients, nosocomial tracheobronchitis has been associated with a longer length of ICU stay and mechanical ventilation, without increased mortality (180). Antibiotic therapy may be beneficial in this group of patients (180, 181). In one prospective randomized trial of intubated patients with community-acquired bronchial infection, the use of antibiotic therapy led to a reduced incidence of subsequent pneumonia and mortality (181).

The diagnosis of HAP is difficult, and most studies of nonintubated patients have involved clinical diagnosis, with sputum culture, but bronchoscopy has been used less often, making the reliability of the bacteriologic information uncertain and the specificity of the diagnosis undefined (182). The accuracy of the clinical diagnosis of VAP has been investigated on the basis of autopsy findings or quantitative cultures of either protected specimen brush (PSB) or bronchoalveolar lavage (BAL) samples as the standard for comparison (183–186). Some studies have investigated the accuracy of a single clinical finding, whereas others included multiple criteria in their definition of pneumonia. These studies indicate that the diagnostic criteria of a radiographic infiltrate and at least one clinical feature (fever, leukocytosis, or purulent tracheal secretions) have high sensitivity but low specificity (especially for VAP). Combinations of signs and symptoms may increase the specificity. A study in which the diagnostic standard was histology plus positive microbiologic cultures of immediate postmortem lung samples, the presence of chest infiltrates, plus two of three clinical criteria resulted in 69% sensitivity and 75% specificity (187). When the three clinical variables were used the sensitivity declined, whereas the use of only one variable led to a decline in specificity.

For patients diagnosed with ARDS, suspicion of pneumonia should be high and the presence of only one of the three clinical criteria described should lead to more diagnostic testing (188). A high index of suspicion should also be present in patients who have unexplained hemodynamic instability or deterioration of blood gases during mechanical ventilation. In the absence of any of these findings, no further investigations are required. The incidence of colonization in hospitalized patients in general and even more in patients requiring endotracheal intubation is high (107). Antibiotic treatment of simple colonization is strongly discouraged. Routine monitoring of tracheal aspirate cultures to anticipate the etiology of a subsequent pneumonia has also been found to be misleading in a significant percentage of cases (189).

Although these criteria should raise suspicion of HAP, confirmation of the presence of pneumonia is much more difficult, and clinical parameters cannot be used to define the microbiologic etiology of pneumonia. The etiologic diagnosis generally requires a lower respiratory tract culture, but rarely may be made from blood or pleural fluid cultures. Respiratory tract cultures can include endotracheal aspirates, BAL or PSB specimens. Overall, the sensitivity of blood cultures is less than 25%, and when positive, the organisms may originate from an extrapulmonary source in a large percentage, even if VAP is also present (190). Although an etiologic diagnosis is made from a respiratory tract culture, colonization of the trachea precedes development of pneumonia in almost all cases of VAP, and thus a positive culture cannot always distinguish a pathogen from a colonizing organism. However, a sterile culture from the lower respiratory tract of an intubated patient, in the absence of a recent change in antibiotic therapy, is strong evidence that pneumonia is not present, and an extrapulmonary site of infection should be considered (191, 192). In addition, the absence of MDR microorganisms from any lower respiratory specimen in intubated patients, in the absence of a change in antibiotics within the last 72 hours, is strong evidence that they are not the causative pathogen. The time course of clearance of these difficult-to-treat microorganisms is usually slow, so even in the face of a recent change in antibiotic therapy sterile cultures may indicate that these organisms are not present (193). For these reasons, a lower respiratory tract sample for culture should be collected from all intubated patients when the diagnosis of pneumonia is being considered. The diagnostic yield and negative

predictive value of expectorated sputum in nonintubated patients have not been determined.

Major Points and Recommendations for Diagnosis

1. All patients should have a comprehensive medical history obtained and undergo physical examination to define the severity of HAP, to exclude other potential sources of infection, and to reveal the presence of specific conditions that can influence the likely etiologic pathogens (**Level II**) (9, 16, 194).
2. All patients should have a chest radiograph, preferably posteroanterior and lateral if not intubated, as portable chest radiographs have limited accuracy. The radiograph can help to define the severity of pneumonia (multilobar or not) and the presence of complications, such as effusions or cavitation (**Level II**) (5, 195).
3. Purulent tracheobronchitis may mimic many of the clinical signs of HAP and VAP, and may require antibiotic therapy, but prospective, randomized trials are needed (**Level III**) (180). Tracheal colonization is common in intubated patients, but in the absence of clinical findings is not a sign of infection, and does not require therapy or diagnostic evaluation (**Level II**) (40, 107).
4. Arterial oxygenation saturation should be measured in all patients to determine the need for supplemental oxygen. Arterial blood gas should be determined if concern exists regarding either metabolic or respiratory acidosis, and this test generally is needed to manage patients who require mechanical ventilation. These results, along with other laboratory studies (complete blood count, serum electrolytes, renal and liver function), can point to the presence of multiple organ dysfunction and thus help define the severity of illness (**Level II**) (38, 188).
5. All patients with suspected VAP should have blood cultures collected, recognizing that a positive result can indicate the presence of either pneumonia or extrapulmonary infection (**Level II**) (190).
6. A diagnostic thoracentesis to rule out a complicating empyema or parapneumonic effusion should be performed if the patient has a large pleural effusion or if the patient with a pleural effusion appears toxic (**Level III**) (5).
7. Samples of lower respiratory tract secretions should be obtained from all patients with suspected HAP, and should be collected before antibiotic changes. Samples can include an endotracheal aspirate, bronchoalveolar lavage sample, or protected specimen brush sample (**Level II**) (183, 184, 192, 196, 197).
8. In the absence of any clinical suspicion of HAP or nosocomial tracheobronchitis, no respiratory tract cultures should be obtained (**Level III**).
9. A sterile culture of respiratory secretions in the absence of a new antibiotic in the past 72 hours virtually rules out the presence of bacterial pneumonia, but viral or *Legionella* infection is still possible (**Level II**) (192). If these patients have clinical signs of infection, an extrapulmonary site of infection should be investigated (**Level II**) (190, 198).
10. For patients with ARDS, for whom it is difficult to demonstrate deterioration of radiographic images, at least one of the three clinical criteria or other signs of pneumonia, such as hemodynamic instability or deterioration of blood gases, should lead to more diagnostic testing (**Level II**) (38).

DIAGNOSTIC STRATEGIES AND APPROACHES

Because clinical suspicion of HAP/VAP is overly sensitive, further diagnostic strategies are required for optimal management. The goals of diagnostic approaches in patients with suspected HAP are to identify which patients have pulmonary infection; to ensure collection of appropriate cultures; to promote the use of early, effective antibiotic therapy, while allowing for streamlining or de-escalation when possible; and to identify patients who have extrapulmonary infection (Figure 1). The committee considered two different approaches to management, a clinical strategy and a bacteriologic strategy, and have incorporated features from both in the final recommendations.

Clinical Strategy

When the clinical approach is used, the presence of pneumonia is defined by new lung infiltrate plus clinical evidence that the infiltrate is of an infectious origin. The presence of a new or progressive radiographic infiltrate plus at least two of three clinical features (fever greater than 38°C, leukocytosis or leukopenia, and purulent secretions) represents the most accurate combination of criteria for starting empiric antibiotic therapy (187). Although sensitivity for the presence of pneumonia is increased if only one criterion is used, this occurs at the expense of specificity, leading to significantly more antibiotic treatment. Requiring all three clinical criteria is too insensitive and will result in many patients with true pneumonia not receiving therapy.

The etiologic cause of pneumonia is defined by semiquantitative cultures of endotracheal aspirates or sputum with initial microscopic examination. Tracheal aspirate cultures consistently grow more microorganisms than do invasive quantitative cultures, and most microbiology laboratories report the results in a semiquantitative fashion, describing growth as light, moderate, or heavy. In general, it is rare that a tracheal aspirate culture does not contain the pathogen(s) found in invasive quantitative cultures (191, 199, 200). Gram staining of polymorphonuclear leukocytes and macrophages and careful examination of the morphology of any bacteria found to be present, may improve diagnostic accuracy when correlated with culture results (201, 202). Conversely, a negative tracheal aspirate (absence of bacteria or inflammatory cells) in a patient without a recent (within 72 hours) change in antibiotics has a strong negative predictive value (94%) for VAP (203). A reliably performed Gram stain of tracheal aspirates has been demonstrated to result in a low incidence of inappropriate therapy when used to guide initial empiric antibiotic therapy (9, 198).

The clinical strategy emphasizes prompt empiric therapy for all patients suspected of having HAP. The driving force behind this strategy is the consistent finding that delay in the initiation of appropriate antibiotic therapy for patients with HAP is associated with increased mortality (37, 112, 204). The selection of initial antibiotic therapy is based on risk factors for specific pathogens, modified by knowledge of local patterns of antibiotic resistance and organism prevalence. Therapy is modified on the basis of the clinical response on Days 2 and 3, and the findings of semiquantitative cultures of lower respiratory tract secretions. This approach requires no specialized microbiologic methods, and all patients suspected of having pneumonia are treated. This avoids the problem of not treating some infected individuals. Use of an ICU-specific, broad-spectrum empiric therapy regiment can reduce the incidence of inappropriate initial therapy to less than 10% (198, 205).

The major limitation to the clinical approach is that it consistently leads to more antibiotic therapy than when therapy decisions are based on the findings (microscopy and quantitative cultures) of invasive (bronchoscopic) lower respiratory tract samples (198). The clinical approach is overly sensitive, and patients can be treated for pneumonia when another noninfectious process is responsible for the clinical findings. These processes may include congestive heart failure, atelectasis, pulmonary thrombo-

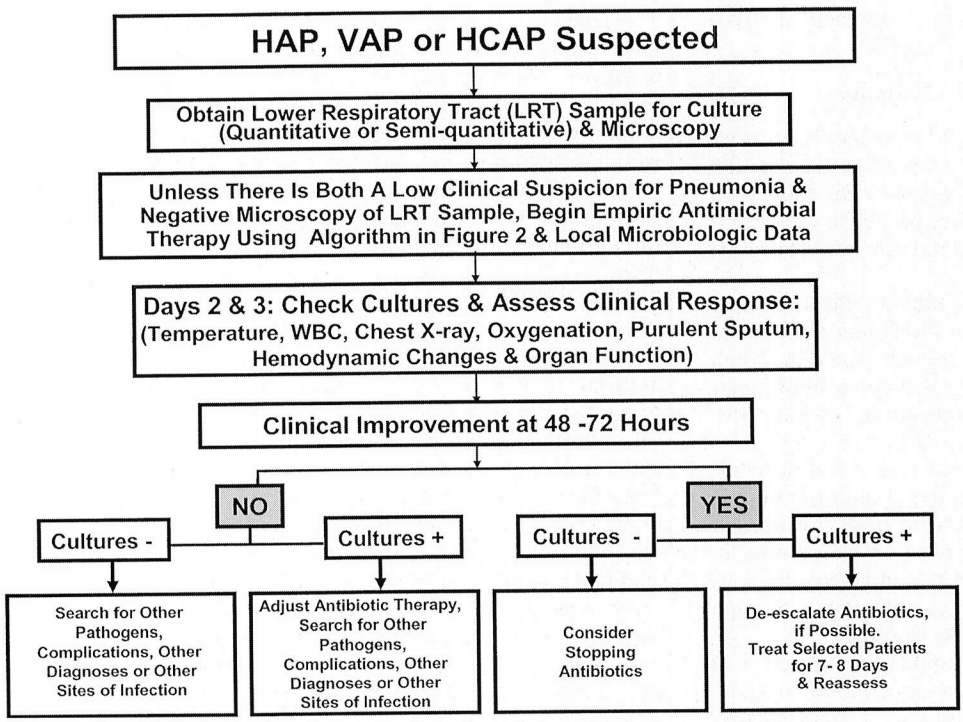

Figure 1. Summary of the management strategies for a patient with suspected hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), or healthcare-associated pneumonia (HCAP). The decision about antibiotic discontinuation may differ depending on the type of sample collected (PSB, BAL, or endotracheal aspirate), and whether the results are reported in quantitative or semiquantitative terms (*see* text for details).

embolism, pulmonary drug reactions, pulmonary hemorrhage, or ARDS. Even if the patient has pneumonia, reliance on semiquantitative cultures, which may not reliably separate true pathogens from colonizers, can lead to either more or broader spectrum antibiotic therapy than with a quantitative approach (198). These cultures have their greatest value if they are negative and the patient has not received new antibiotics within the past 72 hours. One other concern is that reliance on nonquantitative cultures could lead to a failure to recognize extrapulmonary infection at an early time point.

In an effort to improve the specificity of clinical diagnosis, Pugin and coworkers developed the clinical pulmonary infection score (CPIS), which combines clinical, radiographic, physiological (Pa_{O_2}/FI_{O_2}), and microbiologic data into a single numerical result (206). When the CPIS exceeded 6, good correlation with the presence of pneumonia, as defined by quantitative cultures of bronchoscopic and nonbronchoscopic BAL specimens, was found. However, in a subsequent study that used histology plus immediate postmortem quantitative lung cultures as the reference standard, the CPIS had a sensitivity of 77% and a specificity of 42% (187). One prospective study evaluated 79 episodes of suspected VAP, using the CPIS, and compared the findings with diagnoses established by BAL culture. Overall, the sensitivity and specificity of the score were low, although it improved if a Gram stain of a deep respiratory tract culture was added to the evaluation (201).

The original description of the CPIS required microbiologic data, and thus could not be used to screen for HAP. Singh and colleagues used a modified CPIS that did not rely on culture data to guide clinical management (207). Another approach was to calculate the score by using the results of a Gram stain of a BAL specimen or blind protected telescoping catheter sample, and score the findings as either positive or negative. Using this approach, the CPIS for patients with confirmed VAP was significantly higher than the value for nonconfirmed VAP (201).

If a clinical strategy is used, reevaluation of the decision to use antibiotics based on serial clinical evaluations, by Day 3 or sooner, is necessary, because patients who are improving will have signs of a good clinical response by this time point (193, 208). Singh and coworkers have shown that some patients with a low clinical suspicion of VAP (CPIS of 6 or less) can have antibiotics safely discontinued after 3 days, if the subsequent course suggests that the probability of pneumonia is still low (207). The modified CPIS used by Singh and coworkers appears to be an objective measure to define patients who can receive a short duration of therapy.

Major points and recommendations for the clinical strategy.

1. A reliable tracheal aspirate Gram stain can be used to direct initial empiric antimicrobial therapy and may increase the diagnostic value of the CPIS (**Level II**) (191, 199, 201, 209).
2. A negative tracheal aspirate (absence of bacteria or inflammatory cells) in a patient without a recent (within 72 hours) change in antibiotics has a strong negative predictive value (94%) for VAP and should lead to a search for alternative sources of fever (**Level II**) (203).
3. The presence of a new or progressive radiographic infiltrate plus at least two of three clinical features (fever greater than 38°C, leukocytosis or leukopenia, and purulent secretions) represent the most accurate clinical criteria for starting empiric antibiotic therapy (**Level II**) (187).
4. If a clinical strategy is used, reevaluation of the decision to use antibiotics based on the results of semiquantitative lower respiratory tract cultures and serial clinical evaluations, by Day 3 or sooner, is necessary (**Level II**) (193, 205, 207, 208).
5. A modified CPIS of 6 or less for 3 days, proposed by Singh and coworkers, is an objective criterion to select patients at low risk for early discontinuation of empiric treatment of HAP, but still requires validation in patients with more severe forms of VAP (**Level I**) (201, 207).

Bacteriologic Strategy

The bacteriologic strategy uses quantitative cultures of lower respiratory secretions (endotracheal aspirates, BAL or PSB speci-

mens collected with or without a bronchoscope) to define both the presence of pneumonia and the etiologic pathogen. Growth above a threshold concentration is required to diagnose VAP/HAP and to determine the causative microorganism(s). Growth below the threshold is assumed to be due to colonization or contamination. The bacteriologic strategy has been used to guide decisions about whether to start antibiotic therapy, which pathogens are responsible for infection, which antimicrobial agents to use, and whether to continue therapy.

Because the bacteriologic approach emphasizes avoidance of the problem of overtreatment with antibiotics by trying to separate colonizing from infecting pathogens, use of this method has consistently led to finding fewer microorganisms growing above the diagnostic threshold than are present in nonqualitative cultures of tracheal aspirates. When therapy decisions have been based on these data, fewer patients have been treated with antibiotics, and a potentially narrower spectrum of therapy was used, compared with the clinical approach (198, 210). Quantitative cultures have been demonstrated to have good diagnostic utility for the presence of pneumonia, especially in patients with a low or equivocal clinical suspicion of infection (211, 212).

The major concern with the bacteriologic approach is that a false negative culture can lead to a failure to treat either a specific patient or a specific pathogen, and that the results are not always consistent and reproducible (213–215). A major factor causing false negative quantitative cultures is a recent starting of or change in antibiotic therapy, especially in the preceding 24 hours, but up to 72 hours (192, 212). Therefore, ideally all quantitative cultures should be obtained before any antibiotic manipulation. This may not be possible in all situations, and in this setting a change in the diagnostic threshold may be helpful (212). For BAL, use of a threshold 10-fold lower than usual may avoid some false negative results in patients given antibiotics before testing. However, some patients with pneumonia will have culture growth below threshold, even without recent antibiotic changes, especially in early forms of infection (215–217).

Methodologic issues involved in the inconsistent results of published studies have been summarized in a meta-analysis (184). These include the evaluation of patients who did not meet recognized clinical criteria for the presence of pneumonia; prolonged time between the performance of a diagnostic test and the collection of confirmatory histopathologic information; inclusion of patients who had received antibiotic therapy before diagnostic testing, often without correcting for the duration of antibiotic therapy; and inclusion of patients studied by BAL performed with insufficient lavage volume (less than 140 ml). A major problem with all studies of HAP diagnosis is the absence of a "gold standard" with which diagnostic results can be compared. Even the best criteria for the presence of pneumonia, immediate postmortem histologic evaluation with microbiologic confirmation of infection, can be inaccurate. In addition, only a subgroup of patients with severe VAP is included in these types of studies.

In a prospective study of 148 patients receiving mechanical ventilation and in whom infectious pneumonia was suspected, Gibot and coworkers used a rapid immunoblot technique on BAL fluid, and found that levels of soluble triggering receptor expressed on myeloid cells (sTREM-1) were the strongest independent predictor of pneumonia (odds ratio, 41.5) (218). When commercially available, this marker, coupled with the classic clinical criteria and results of microbiologic cultures, may be a valuable tool with which to increase the specificity and maintain the sensitivity of HAP diagnosis (197).

Histologic data have demonstrated several characteristics of VAP pertinent to diagnostic testing, such as the finding that the process is often multifocal, frequently involving both lungs, generally in the posterior and lower segments (191, 215, 216). Postmortem studies have also demonstrated that VAP is often in multiple different phases of evolution at different sites at the same time (216). Prior antibiotic therapy can influence the number of bacteria found in lung tissue, and patients who have died in spite of prolonged therapy are likely to have organisms resistant to the agents used, whereas patients started on therapy within 24 (and up to 72) hours may have negative cultures, especially if the therapy is adequate (192). The multifocal nature of VAP suggests that BAL and endotracheal aspirates can provide more representative samples than the protected specimen brush (PSB), which samples only a single bronchial segment. Because of the diffuse bilateral nature of VAP and predominance in dependent lung segments, "blind" BAL and PSB may be as accurate as bronchoscopic sampling in some patients (219).

Another issue with the bacteriologic strategy is that culture results are not available immediately. Ancillary tests such as Giemsa stain for intracellular microorganisms, Gram stain, or differential cell counts can be used to increase the likelihood of a subsequent positive culture and can be used to guide the need for antibiotic therapy before culture results. In some studies, this approach has led to less use of antibiotics with no adverse outcomes, and a tendency to improved mortality (198, 201). Not all investigators agree about the safety of withholding therapy until quantitative results are available, and are positive, or to withdrawing therapy if cultures are negative, after empirically starting antimicrobials for suspected infection (198, 220–222). Clinically, these decisions have been guided by the degree of certainty of the diagnosis of pneumonia at the time of testing (pretest probability), and on the severity of illness of the patient (198). Thus, most investigators agree that patients with signs of infection, who are clinically unstable, should receive therapy, regardless of the initial bronchoscopic findings (198, 212).

The diagnostic threshold to discriminate infection from colonization varies with the technique used, and possibly by the clinical probability of infection (212). The threshold may be lowered if the patient has recently had a change in antibiotic therapy or if the probability of infection is high. Endotracheal aspirates can be cultured quantitatively, and with a threshold of 10^6 cfu/ml or more the sensitivity of this method for the presence of pneumonia has varied from 38 to 82%, with a mean of 76 ± 9%, and with a specificity ranging from 72 to 85%, with a mean of 75 ± 28% (209).

Bronchoscopic BAL studies have typically used a diagnostic threshold of 10^4 or 10^5 cfu/ml. Samples contaminated by upper airway secretions, as reflected by a high percentage of squamous epithelial cells, should be used with caution. A few studies have shown the technique to be reproducible, but not all bacteria are recovered above the diagnostic threshold when the procedure has been repeated in the same patient at the same site (223). An evidence-based review of 23 prospective studies of BAL in suspected VAP showed a sensitivity of 42–93%, with a mean of 73 ± 18% (186), and a specificity of 45–100%, with a mean of 82 ± 19%. In 12 studies, the detection of intracellular organisms in 2–5% of recovered cells was used to diagnose pneumonia, with a mean sensitivity of 69 ± 20% and a specificity of 75 ± 28% (186). The advantage of looking for intracellular organisms is the ability to obtain information of high predictive value in a rapid time frame, without waiting for the results of cultures to define the presence of pneumonia, although not the specific identity of the etiologic pathogen.

Quantitative cultures of PSB samples have used a diagnostic threshold of 10^3 cfu/ml or more. The quality of the PSB sample is difficult to measure, and the reproducibility is not exact, with as many as 25% of results on different sides of the diagnostic threshold, when comparing two samples collected from the same site in the same patient (183). The sensitivity and specificity range

from 33 to 100% (mean, 66 ± 19%) and from 50 to 100% (mean, 90 ± 15%). PSB appears to be more specific than sensitive for the presence of pneumonia, and a positive result greatly increases the likelihood of pneumonia being present (186).

The bacteriologic strategy does require specialized laboratory and clinical skills. In many clinical settings, bronchoscopy is not immediately available, especially in the evenings, and the collection of blind, nonbronchoscopic samples is an appealing alternative. Blind sampling can be done by BAL or PSB, or a blind bronchial suction sample can be taken. When BAL samples are obtained nonbronchoscopically, the threshold varies by technique and may be different from that of bronchoscopic BAL. The sensitivities of blind bronchial suction, blind mini-BAL, and blind PSB are 74–97, 63–100, and 58–86%, respectively (224). The specificity of these methods has varied from 74 to 100% for blind bronchial suction, from 66 to 96% for mini-BAL, and from 71 to 100% for blind PSB. In general, these techniques provide data similar to those of samples collected bronchoscopically, although with a trend toward more cultures above the diagnostic threshold. Side effects should be no greater and possibly less than with bronchoscopically collected samples.

Recommendation for the bacteriologic strategy. Quantitative cultures can be performed on endotracheal aspirates or samples collected either bronchoscopically or nonbronchoscopically, and each technique has its own diagnostic threshold and methodologic limitations. The choice of method depends on local expertise, experience, availability, and cost (**Level II**) (197, 198, 214, 224).

Recommended Diagnostic Strategy

To date, several decision analyses, one retrospective study, and four prospective studies have evaluated the impact of diagnostic strategies on the use of antibiotics and the outcomes of patients with suspected VAP (198, 211, 212, 220–222, 225). In three randomized single-center studies, no differences in mortality were found when invasive techniques (PSB and/or BAL) were compared with either quantitative or semiquantitative endotracheal aspirate culture techniques (220–222). However, these studies included few patients (51, 76, and 88, respectively) and antibiotics were continued in all patients, even those with negative cultures, thereby negating one of the potential advantages of the bacteriologic strategy. In fact, several prospective studies have concluded that antibiotics can be safely stopped in patients with negative quantitative cultures, with no adverse impact on mortality (15, 198, 226).

One large, prospective randomized trial did show an advantage to the quantitative bronchoscopic approach, when compared with a clinical approach in a multicenter study of 413 patients suspected of having HAP (198). Compared with patients managed clinically, those receiving invasive management had a lower mortality rate on Day 14 (16 and 25%; $p = 0.02$), but not on Day 28, and lower mean sepsis-related organ failure assessment scores on Days 3 and 7 ($p = 0.04$). At 28 days, the quantitative culture group had significantly more antibiotic-free days (11 ± 9 versus 7 ± 7 days; $p < 0.001$), but only a multivariate analysis showed a significant difference in mortality (hazard ratio, 1.54; 95% confidence interval, 1.10 to 2.16; $p = 0.01$). One strength of the study was that a high percentage of patients in both arms received adequate initial antibiotics, although more patients in the invasive group received adequate therapy than in the clinical group, and the impact of this difference on the observed mortality differences was uncertain. Another important consequence of quantitative culture results was that the presence of clinical signs of infection in patients with negative cultures was often an indication that an extrapulmonary site of infection was present. This study clearly showed that the quantitative approach could be applied safely, leading to less antibiotic use, and potentially reducing mortality. In the trial, about 10% of the patients managed with a quantitative strategy received antibiotic therapy regardless of bronchoscopic findings because of the presence of clinical instability and signs of sepsis.

Considering the available methods for diagnostic testing and the goals of using appropriate therapy in a timely manner, without overusing antibiotics, the committee has combined features of the clinical and bacteriologic approach into an algorithm shown in Figure 1. The decision to discontinue antibiotics, using this algorithm, may differ depending on the type of respiratory tract sample that is collected and whether the culture results are reported in quantitative or semiquantitative terms. Advocates of the bacteriologic approach support the discontinuation of antibiotics in clinically stable patients whose quantitative culture results of deep lung samples (BAL or PSB) fall below a diagnostic threshold. The utility of quantitative endotracheal aspirates for this decision is not as well defined. Advocates of the clinical strategy generally make a decision about antibiotic discontinuation based on the clinical course of the patient, supplemented by data from either quantitative or semiquantitative cultures from a lower respiratory tract sample, which could include an endotracheal aspirate, as well as a BAL or PSB sample.

Major Points and Recommendations for Comparing Diagnostic Strategies

1. A patients with suspected VAP should have a lower respiratory tract sample sent for culture, and extrapulmonary infection should be excluded, as part of the evaluation before administration of antibiotic therapy (**Level II**) (198).
2. If there is a high pretest probability of pneumonia, or in the 10% of patients with evidence of sepsis, prompt therapy is required, regardless of whether bacteria are found on microscopic examination of lower respiratory tract samples (**Level II**) (197, 198).
3. Diagnostic techniques that identify etiologic pathogens on the basis of qualitative cultures will lead to therapy for more organisms than diagnostic techniques based on quantitative cultures (**Level I**) (198, 220–222).
4. Semiquantitative cultures of tracheal aspirates cannot be used as reliably as quantitative cultures to define the presence of pneumonia and the need for antibiotic therapy (**Level I**) (198, 220–222).
5. If bronchoscopic sampling is not immediately available, nonbronchoscopic sampling can reliably obtain lower respiratory tract secretions for quantitative cultures, which can be used to guide antibiotic therapy decisions (**Level II**) (224).
6. The use of a bronchoscopic bacteriologic strategy has been shown to reduce 14-day mortality, compared with a clinical strategy, in one study of suspected VAP (**Level I**) (198).
7. Delays in the initiation of appropriate antibiotic therapy can increase the mortality of VAP and thus therapy should not be postponed for the purpose of performing diagnostic studies in patients who are clinically unstable (**Level II**) (37, 111, 198).

ANTIBIOTIC TREATMENT OF HOSPITAL-ACQUIRED PNEUMONIA

General Approach

Once the clinical decision has been made to initiate therapy, the overall approach to therapy for suspected HAP is shown in

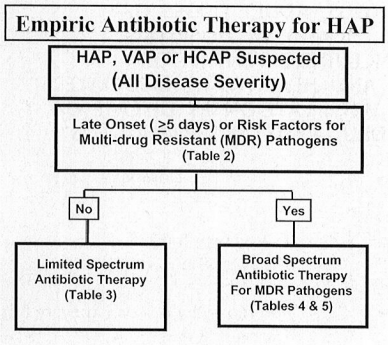

Figure 2. Algorithm for initiating empiric antibiotic therapy for hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), and healthcare-associated pneumonia (HCAP).

Figure 2. Antibiotic selection for each patient should be based on the risk factors for MDR pathogens summarized in Table 2. The algorithms shown in Figures 1 and 2 provide the pathways for selection of appropriate antibiotics for the initial management of HAP, VAP, and HCAP on the basis of time of onset of disease and risk for MDR pathogens, as outlined in Tables 3 and 4. The adequate dosing of antibiotics for empiric therapy for MDR pathogens is summarized in Table 5. Broad-spectrum empiric antibiotic therapy should be accompanied by a commitment to deescalate antibiotics, on the basis of serial clinical and microbiologic data, to limit the emergence of resistance in the hospital.

The antimicrobial spectrum of activity, effective doses of antibiotics, pharmacokinetic profiles, adverse effects of individual antimicrobials, and the role of monotherapy were carefully reviewed by the consensus committee. Whenever possible, antibiotic recommendations were based on well-designed, controlled clinical trials, but when such data were not available, then the spectrum of activity, pharmacokinetic data, and reported clinical experience were taken into account. These initial empiric therapy recommendations require modification based on knowledge of the predominant pathogens in any specific clinical setting and the local patterns of antibiotic susceptibility. In addition, once the results of respiratory tract and blood cultures become available, therapy can often be focused or narrowed (i.e., de-escalation) on the basis of the identity of specific pathogens and their susceptibility to specific antibiotics (Figure 1). The algorithm shown in Figure 2 will lead to many patients receiving an initial broad-spectrum therapy, because risk factors for MDR pathogens are common, and thus it is important to use serial clinical evaluations and microbiologic data to deescalate therapy whenever possible.

Initial Empiric Antibiotic Therapy

The key decision in initial empiric therapy is whether the patient has risk factors for MDR organisms. Previously, the time of onset of HAP was used to classify patients as either "early onset" or "late onset," depending on whether the infection began within the first 4 days of hospitalization or later (5). However, many patients are admitted after a recent hospitalization or from a healthcare-associated facility (nursing home, dialysis center, etc.). These patients should be classified as at risk for MDR pathogens, regardless of when in the time course of the current hospitalization the pneumonia begins. Healthcare-associated infections are bacteriologically similar to hospital-acquired infections (4, 6, 43, 227). HCAP is defined by a positive respiratory tract culture, obtained within 48 hours of hospital admission, in a patient who has the criteria listed in Table 2 (43). Most patients with HCAP are at risk for infection with MDR organisms, but in studies of HAP and VAP, hospitalization for at least 5 days is required to increase the risk of infection with these organisms (21, 103).

One of the consequences of increasing antimicrobial resistance is an increased probability of inappropriate initial empiric antimicrobial treatment of infections (228). Inappropriate antimicrobial treatment represents the use of antibiotics with poor or no *in vitro* activity against the identified microorganisms causing infection at the tissue site of infection (e.g., empiric treatment with nafcillin for pneumonia subsequently documented to be MRSA). Because delays in the administration of appropriate therapy have been associated with excess hospital mortality from HAP (37, 111, 112, 229, 230), the prompt administration of empiric therapy for patients likely to have VAP is essential. Alvarez-Lerma showed that, among 490 episodes of pneumonia acquired in the ICU setting, 214 episodes (43.7%) required modification of the initial antibiotic regimen due to either isolation of a resistant microorganism (62.1%) or lack of clinical response to therapy (36.0%) (204). Attributable mortality from HAP was significantly lower among patients receiving initial appropriate antibiotic treatment compared with patients requiring a treatment change (16.2 versus 24.7%; $p = 0.034$).

Iregui and coworkers also documented an adverse outcome with initially delayed appropriate antimicrobial therapy in 107 patients with VAP and examined factors leading to such delays (112). Thirty-three (30.8%) patients received appropriate antibiotic treatment that was delayed 24 hours or more after patients initially met diagnostic criteria for VAP, often because of a delay in physician recognition of the presence of VAP and writing the orders for antimicrobial treatment (n = 25; 75.8%). Patients receiving delayed antimicrobial treatment had greater hospital

TABLE 3. INITIAL EMPIRIC ANTIBIOTIC THERAPY FOR HOSPITAL-ACQUIRED PNEUMONIA OR VENTILATOR-ASSOCIATED PNEUMONIA IN PATIENTS WITH NO KNOWN RISK FACTORS FOR MULTIDRUG-RESISTANT PATHOGENS, EARLY ONSET, AND ANY DISEASE SEVERITY

Potential Pathogen	Recommended Antibiotic*
Streptococcus pneumoniae†	Ceftriaxone
Haemophilus influenzae	*or*
Methicillin-sensitive *Staphylococcus aureus*	Levofloxacin, moxifloxacin, or ciprofloxacin
Antibiotic-sensitive enteric gram-negative bacilli	*or*
Escherichia coli	Ampicillin/sulbactam
Klebsiella pneumoniae	*or*
Enterobacter species	Ertapenem
Proteus species	
Serratia marcescens	

* *See* Table 5 for proper initial doses of antibiotics.

† The frequency of penicillin-resistant *S. pneumoniae* and multidrug-resistant *S. pneumoniae* is increasing; levofloxacin or moxifloxacin are preferred to ciprofloxacin and the role of other new quinolones, such as gatifloxacin, has not been established.

TABLE 4. INITIAL EMPIRIC THERAPY FOR HOSPITAL-ACQUIRED PNEUMONIA, VENTILATOR-ASSOCIATED PNEUMONIA, AND HEALTHCARE-ASSOCIATED PNEUMONIA IN PATIENTS WITH LATE-ONSET DISEASE OR RISK FACTORS FOR MULTIDRUG-RESISTANT PATHOGENS AND ALL DISEASE SEVERITY

Potential Pathogens	Combination Antibiotic Therapy*
Pathogens listed in Table 3 and MDR pathogens *Pseudomonas aeruginosa* *Klebsiella pneumoniae* (ESBL$^+$)† *Acinetobacter* species†	Antipseudomonal cephalosporin (cefepime, ceftazidime) *or* Antipseudomonal carbepenem (imipenem or meropenem) *or* β-Lactam/β-lactamase inhibitor (piperacillin–tazobactam) *plus* Antipseudomonal fluoroquinolone† (ciprofloxacin or levofloxacin) *or* Aminoglycoside (amikacin, gentamicin, or tobramycin) *plus*
Methicillin-resistant *Staphylococcus aureus* (MRSA) *Legionella pneumophila*†	Linezolid or vancomycin‡

* *See* Table 5 for adequate initial dosing of antibiotics. Initial antibiotic therapy should be adjusted or streamlined on the basis of microbiologic data and clinical response to therapy.

† If an ESBL$^+$ strain, such as *K. pneumoniae*, or an *Acinetobacter* species is suspected, a carbepenem is a reliable choice. If *L. pneumophila* is suspected, the combination antibiotic regimen should include a macolide (e.g., azithromycin) or a fluoroquinolone (e.g., ciprofloxacin or levofloxacin) should be used rather than an aminoglycoside.

‡ If MRSA risk factors are present or there is a high incidence locally.

TABLE 5. INITIAL INTRAVENOUS, ADULT DOSES OF ANTIBIOTICS FOR EMPIRIC THERAPY OF HOSPITAL-ACQUIRED PNEUMONIA, INCLUDING VENTILATOR-ASSOCIATED PNEUMONIA, AND HEALTHCARE-ASSOCIATED PNEUMONIA IN PATIENTS WITH LATE-ONSET DISEASE OR RISK FACTORS FOR MULTIDRUG-RESISTANT PATHOGENS

Antibiotic	Dosage*
Antipseudomonal cephalosporin	
Cefepime	1–2 g every 8–12 h
Ceftazidime	2 g every 8 h
Carbepenems	
Imipenem	500 mg every 6 h or 1 g every 8 h
Meropenem	1 g every 8 h
β-Lactam/β-lactamase inhibitor	
Piperacillin–tazobactam	4.5 g every 6 h
Aminoglycosides	
Gentamicin	7 mg/kg per d†
Tobramycin	7 mg/kg per d†
Amikacin	20 mg/kg per d†
Antipseudomonal quinolones	
Levofloxacin	750 mg every d
Ciprofloxacin	400 mg every 8 h
Vancomycin	15 mg/kg every 12 h‡
Linezolid	600 mg every 12 h

* Dosages are based on normal renal and hepatic function.

† Trough levels for gentamicin and tobramycin should be less than 1 μg/ml, and for amikacin they should be less than 4–5 μg/ml.

‡ Trough levels for vancomycin should be 15–20 μg/ml.

mortality compared with patients without the delay (69.7 versus 28.4%; $p < 0.001$). Delays in the administration of appropriate antibiotic treatment have also been associated with greater mortality for patients with severe sepsis, and with greater hospital costs and lengths of stay for patients with VAP (231, 232). A consistent factor leading to delays in appropriate therapy in these studies is the presence of resistant organisms, once again emphasizing the need to anticipate these pathogens in the selection of initial therapy in at-risk patients (205, 228).

Changing antimicrobial therapy once culture results are available may not reduce the excess risk of hospital mortality associated with inappropriate initial antibiotic therapy treatment (37, 204, 233). Therefore, selection of initial appropriate therapy (i.e., getting the antibiotic treatment right the first time) is an important aspect of care for hospitalized patients with serious infections. The regimens and adequate doses listed in Table 5 are therefore directed at the pathogens commonly associated with inappropriate initial empiric antimicrobial therapy. The most common pathogens include *P. aeruginosa*, *Acinetobacter* species, *K. pneumoniae*, *Enterobacter* species, and MRSA (37, 111, 204, 228–230, 233). Patients at risk for infection with these organisms should initially receive a combination of agents that can provide a broad spectrum of coverage to minimize the potential for inappropriate antibiotic treatment. In the therapy of suspected pseudomonal infection, therapy should involve a selected β-lactam plus either an antipseudomonal quinolone or an aminoglycoside. The choice of agents should be based on local patterns of antimicrobial susceptibility, and anticipated side effects, and should also take into account which therapies patients have recently received (within the past 2 weeks), striving not to repeat the same antimicrobial class, if possible.

For the initial antimicrobial therapy regimen to account for local bacteriologic patterns, each hospital and each ICU should ideally have their own antibiogram, which is updated as often as possible. Variability in the microorganisms associated with hospital-acquired infections among hospitals, as well as within the wards of large hospitals, has been demonstrated to occur (41, 234). In addition, changing temporal patterns of nosocomial pathogens and antimicrobial susceptibility have been described (235). Having current, and frequently updated, knowledge of such data can increase the likelihood that appropriate initial antibiotic treatment will be prescribed (205, 235).

When patients at risk for infection with MDR pathogens are identified, empiric therapy should be with agents that are known to be effective against these organisms. Trouillet and coworkers found that 57% of 135 consecutive episodes were caused by "potentially resistant" organisms (21). According to logistic regression analysis, three variables predicted potentially drug-resistant bacterial etiology for VAP: duration of mechanical ventilation, 7 days or more (odds ratio, 6.0); prior antibiotic use (odds ratio, 13.5); and prior use of broad-spectrum drugs (third-generation cephalosporin, fluoroquinolone, and/or a carbapenem) (odds ratio, 4.1). Of 15 different antimicrobial regimens, the combination of a carbapenem, amikacin, and vancomycin provided the broadest *in vitro* coverage against the spectrum of bacteria found in their ICU. Ibrahim and coworkers found that initial coverage for *P. aeruginosa* and methicillin-resistant *S. aureus* (MRSA), the two most common pathogens causing VAP in their ICU, required combination antimicrobial treatment with vancomycin, a carbapenem, and a fluoroquinolone to provide *in vitro* coverage for more than 90% of all the bacterial isolates (205). These studies suggest that each ICU should collect similar data to establish its own "best empiric therapy regimen," tailored to the antibiotic susceptibility patterns of the local flora.

If patients develop HAP during or shortly after antibiotic treatment for a different infection, the empiric therapy should probably involve an agent from a different antibiotic class. Recent exposure to a class of antibiotics can predict subsequent resistance to a variety of agents, usually to the same class but occasionally to other classes of agents as well (236).

Protocols for initial empiric therapy have emerged as a potentially effective means of avoiding unnecessary antibiotic administration while increasing the likelihood of initially appropriate therapy. The potential benefits of antibiotic therapy guidelines, through the use of a computerized system guiding antibiotic choice based on knowledge of local microbiology and general pharmacologic principles, have been demonstrated (113). This system reduced inappropriate empiric antibiotic administration compared with individual physician prescribing practices (237). Use of the automated guideline also significantly reduced orders for drugs to which patients were allergic, reduced overall adverse antibiotic-related events, reduced the total number of antiinfective doses prescribed, as well as reduced the medical costs associated with antimicrobial agents (113).

Nonautomated or partially automated protocols, often driven by hospital-based quality improvement teams, have also demonstrated efficacy. Bailey and coworkers randomized patients in two teaching hospitals to have their physicians contacted by pharmacists with consensus recommendations to discontinue intravenous antibiotics versus no intervention (238). The intervention significantly reduced antibiotic doses administered and mean antibiotic costs but was associated with increased labor costs. Similarly, Leibovici and coworkers developed a problem-oriented database decision support system that significantly reduced the unnecessary use of antibiotics and decreased inappropriate antibiotic administration, particularly to patients infected with multidrug-resistant gram-negative isolates, enterococci, and *S. aureus* (239).

Ibrahim and coworkers compared the management of 50 patients with VAP in a time period without an antibiotic protocol with 52 patients with VAP who were managed by an ICU-specific protocol (205). The protocol-directed therapy required initial intravenous combination antimicrobial treatment with vancomycin, imipenem, and ciprofloxacin. The guideline also required that after 48 hours antibiotic treatment be modified on the basis of the available culture results. De-escalation was achieved in 61.5% of patients. An additional feature of the protocol was an attempt to limit therapy to a 7-day course of appropriate antibiotic(s) for patients with VAP. Administration of antimicrobials beyond Day 7 was recommended only for patients with persistent signs and symptoms consistent with active infection (e.g., fever greater than 38.3°C, circulating leukocyte count greater than 10,000 mm^{-3}, lack of improvement on the chest radiograph, continued purulent sputum). Use of the guideline was associated with a statistically significant increase in the administration of appropriate antimicrobial treatment and a decrease in the development of secondary episodes of antibiotic-resistant VAP. A significant reduction in the total duration of antimicrobial treatment to 8.1 ± 5.1 days from 14.8 ± 8.1 days ($p < 0.001$) was achieved.

Major points and recommendations for initial antibiotic therapy.

1. Use the algorithm in Figure 2 to select an initial empiric therapy based on the absence or presence of risk factors for MDR pathogens (Tables 2–4) (**Level III**). These risk factors include prolonged duration of hospitalization (5 days or more), admission from a healthcare-related facility, and recent prolonged antibiotic therapy (**Level II**) (21, 43).
2. Choice of specific agents should be dictated by local microbiology, cost, availability, and formulary restrictions (**Level II**) (41, 205, 234).
3. Patients with healthcare-related pneumonia should be treated for potentially drug-resistant organisms, regardless of when during the hospital stay the pneumonia begins (**Level II**) (43).
4. Inappropriate therapy (failure of the etiologic pathogen to be sensitive to the administered antibiotic) is a major risk factor for excess mortality and length of stay for patients with HAP, and antibiotic-resistant organisms are the pathogens most commonly associated with inappropriate therapy (**Level II**) (228).
5. In selecting empiric therapy for patients who have recently received an antibiotic, an effort should be made to use an agent from a different antibiotic class, because recent therapy increases the probability of inappropriate therapy and can predispose to resistance to that same class of antibiotics (**Level III**) (236).
6. Initial antibiotic therapy should be given promptly because delays in administration may add to excess mortality resulting from VAP (**Level II**) (37, 112, 231, 232).
7. Initial empiric therapy is more likely to be appropriate if a protocol for antibiotic selection is developed on the basis of the recommendations in Tables 2–4, but adapted to local patterns of antibiotic resistance, with each ICU collecting this information and updating it on a regular basis (**Level II**) (205).

Appropriate Antibiotic Selection and Adequate Dosing

Optimal outcome in patients with HAP can best be achieved with the combination of appropriate initial therapy (the etiologic organism is sensitive to the therapeutic agent) and an adequate therapy regimen. To achieve adequate therapy, it is necessary not only to use the correct antibiotic, but also the optimal dose and the correct route of administration (oral, intravenous, or aerosol) to ensure that the antibiotic penetrates to the site of infection, and to use combination therapy if necessary. In the management of VAP, it is important to use doses of antibiotics that have been shown in clinical trials to have efficacy. Thus, for the empiric therapy of severe VAP, the correct doses of commonly used agents for patients with normal renal function are shown in Table 5 (240–247).

Pharmacodynamic properties of specific antibiotics should also be considered in selecting an adequate dosing regimen. Some antibiotics penetrate well and achieve high local concentrations in the lung whereas others do not. For example, most β-lactam antibiotics achieve less than 50% of their serum concentration in the lung, whereas fluoroquinolones and linezolid equal or exceed their serum concentration in bronchial secretions (5, 248). The relevance of these findings to outcomes in therapy remains to be defined.

The mechanism of action of certain agents can also affect dosing regimens, efficacy, and toxicity. Some antimicrobials are bactericidal whereas others are bacteriostatic. Even among the bactericidal agents, several mechanisms of killing can be present. Agents such as the aminoglycosides and quinolones are bactericidal in a concentration-dependent fashion, killing more rapidly at high concentrations. Other agents, such as vancomycin and the β-lactams, are also bactericidal, but in a more time-dependent fashion, with the degree of killing dependent on the time that the serum concentration is above the organism's minimal inhibitory concentration (MIC). Another difference is that some antibiotics have a "postantibiotic effect" (PAE), which means that these agents are able to suppress bacterial growth even after the antibiotic level falls below the MIC of the organism (5, 249, 250). With gram-negative bacilli, a prolonged PAE occurs with the use of aminoglycosides and quinolones. No PAE, or a short PAE against gram-negative bacilli, is seen with β-lactam antibiotics. One exception is the carbepenem antibiotics (imipenem or meropenem), which have shown a postantibiotic effect against gram-negative bacilli such as *P. aeruginosa* (5, 251).

These pharmacodynamic effects lead to drug-specific dosing regimens. The β-lactams, with minimal concentration-dependent killing and a limited postantibiotic effect, are most effective if levels stay above the MIC of the infecting organism for as long as possible

(247). This requires frequent dosing, or even continuous infusion. On the other hand, quinolones and aminoglycosides can be dosed less often because of the prolonged postantibiotic effect. In addition, because of their concentration-dependent killing mechanism, efficacy may be improved by using a regimen that maximizes initial serum concentrations. Combining an entire day of therapy into a single daily (every 24 hours) dose can take advantage of both the concentration-dependent killing mechanism and the postantibiotic effect. This type of dosing regimen has been applied to the aminoglycosides to maximize efficacy and minimize toxicity, but clinical trials have produced conflicting results about the success of achieving these goals (252).

All patients with HAP and VAP should initially receive therapy intravenously, but conversion to oral/enteral therapy may be possible in certain responding patients. The quinolones and linezolid have oral formulations with bioavailability equivalent to the intravenous form, and this may facilitate conversion to oral therapy in patients with a good clinical response (below) and intact gastrointestinal tract function. Studies with quinolones have shown that early step-down to oral therapy is safe and effective (253, 254).

Local Instillation and Aerosolized Antibiotics

Local instillation or aerosolization is a way to enhance antibiotic penetration to the lower respiratory tract. In the past, the agents most commonly administered and studied in this fashion have been the aminoglycosides and polymyxin B (255, 256). Only a single prospective randomized trial has examined the impact of the adjunctive use of locally instilled tobramycin with intravenous therapy in the treatment of VAP (256). Although the addition of endotracheal tobramycin did not improve clinical outcome compared with placebo, microbiologic eradication was significantly greater in the patients receiving aerosolized antibiotics. The small number of patients in this study suggests that more data are needed on this type of therapy before determining its value.

Aerosolized antibiotics may also be useful to treat microorganisms that, on the basis of high MIC values, are "resistant" to systemic therapy. Anecdotal reports have appeared of patients with VAP due to MDR *P. aeruginosa* that is unresponsive to systemic antibiotics, but who have improved with the addition of aerosolized aminoglycosides or polymyxin B (255). Concern about aerosolized antibiotics leading to an increased risk of pneumonia due to resistant microorganisms was raised when these agents were used as prophylaxis, not as therapy (257). One side effect of aerosolized antibiotics has been bronchospasm, which can be induced by the antibiotic or the associated diluents present in certain preparations. The committee believed that further investigation into the use of aerosolized antibiotics is warranted.

Combination versus Monotherapy

Combination therapy is common practice in the therapy of suspected and proven gram-negative HAP. The commonly cited reason to use combination therapy is to achieve synergy in the therapy of *P. aeruginosa*. However, synergy has been clearly documented to be valuable only *in vitro* and in patients with neutropenia or bacteremic infection, which is uncommon in VAP (5, 258). The *in vitro* finding of synergy has been inconsistently demonstrated, and has been difficult to show as being clinically relevant (258, 259).

Combination regimens have also been recommended as a method to prevent the emergence of resistance during therapy, a common phenomenon when *P. aeruginosa* is treated with a variety of single agents and when *Enterobacter* is treated with third-generation cephalosporins (240, 260). Prevention of this type of antibiotic resistance by combination therapy has not been well documented (261). A metaanalysis has evaluated all prospective randomized trials of β-lactam monotherapy compared with β-lactam–aminoglycoside combination regimens in patients with sepsis, of whom at least 1,200 of the reported 7,586 patients had either HAP or VAP (262). In this evaluation, clinical failure was more common with combination therapy and there was no advantage in the therapy of *P. aeruginosa* infections, compared with monotherapy. In addition, combination therapy did not prevent the emergence of resistance during therapy, but did lead to a significantly higher rate of nephrotoxicity.

However, in spite of these data, another reason to use combination therapy, especially for the patients treated according to the regimens in Table 4, is to provide a broad-spectrum empiric regimen that is likely to include at least one drug that is active against the often MDR etiologic agent(s). Combination therapy should include agents from different antibiotic classes to avoid antagonism of therapeutic mechanisms. For gram-negatives, regimens usually involve combinations of two drugs from the β-lactam, quinolone, or aminoglycoside classes. Although quinolones can penetrate into the lung better than aminoglycosides and have less potential for nephrotoxicity, a trend toward improved survival has been seen with aminoglycoside-containing, but not with quinolone-containing, combinations (259). In some studies, combination therapy has been continued for less than the full course of therapy, with discontinuation of the aminoglycoside after 5 days if the patient is improving (235).

Monotherapy should be used when possible because combination therapy is often expensive and exposes patients to unnecessary antibiotics, thereby increasing the risk of MDR pathogens and adverse outcomes. Patients who develop nosocomial pneumonia with no risk factors for drug-resistant organisms are likely to respond to monotherapy with the antibiotics listed in Table 3. Monotherapy is also the standard when gram-positive HAP, including MRSA, is documented. Monotherapy with ciprofloxacin has been successful in patients with mild HAP (defined as a CPIS of 6 or less) but is less effective in severe HAP (207, 240). Agents that have been shown to be effective as monotherapy in patients with moderately severe HAP not due to MDR pathogens include ciprofloxacin, levofloxacin, imipenem, meropenem, cefepime, and piperacillin–tazobactam (240, 242–247). For monotherapy, these agents must be dosed optimally, as discussed above. To use monotherapy in patients with severe VAP, the committee believed that patients should initially receive combination therapy as described in Table 4, but therapy could be focused to a single agent if lower respiratory tract cultures did not demonstrate a resistant pathogen (205).

Duration of Therapy

Efforts to reduce the duration of therapy for VAP are justified by studies of the natural history of the response to therapy. Dennesen and colleagues demonstrated that when VAP was caused by *H. influenzae* and *S. pneumoniae*, the organisms could be rapidly eradicated from tracheal aspirates, whereas Enterobacteriaceae, *S. aureus*, and *P. aeruginosa* persisted despite *in vitro* susceptibility to the antibiotics administered (193). Significant improvements were observed for all clinical parameters, generally within the first 6 days of the start of antibiotics. The consequence of prolonged therapy to 14 days or more was newly acquired colonization, especially with *P. aeruginosa* and Enterobacteriaceae, generally during the second week of therapy. Luna and coworkers, using serial CPIS measurements, found that patients who survived VAP after receiving adequate therapy tended to have a clinical improvement by Days 3–5, especially reflected by improved Pa_{O_2}/FI_{O_2} ratio, whereas nonresponding patients did not have such a response during the same time period (208). These data support the premise that most patients with VAP, who receive appropriate antimicrobial therapy, have a good clinical response within the first 6 days. Prolonged therapy

simply leads to colonization with antibiotic resistant bacteria, which may precede a recurrent episode of VAP.

Reducing the duration of therapy in patients with VAP has led to good outcomes with less antibiotic use with a variety of different strategies. Singh and coworkers used a modification of the CPIS system to identify low-risk patients (CPIS of 6 or less) with suspected VAP who could be treated with 3 days of antibiotics as opposed to the conventional practice of 10 to 21 days of antibiotic therapy (207). Patients receiving the shorter course of antibiotic therapy had better clinical outcomes than patients receiving longer therapy, with fewer subsequent superinfections attributed to antibiotic-resistant pathogens, although many of these patients may not have had pneumonia. A multicenter, randomized, controlled trial demonstrated that patients who received appropriate, initial empiric therapy of VAP for 8 days had outcomes similar to those of patients who received therapy for 14 days (210). A trend to greater rates of relapse for short-duration therapy was seen if the etiologic agent was *P. aeruginosa* or an *Acinetobacter* species.

Major Points and Recommendations for Optimal Antibiotic Therapy

1. Empiric therapy of patients with severe HAP or VAP requires the use of antibiotics at optimal doses, to ensure maximum efficacy (**Level I**) (240, 242–247). Initial therapy should be administered to all patients intravenously, with a switch to oral/enteral therapy in selected patients with a good clinical response and a functioning intestinal tract. Highly bioavailable agents, such as the quinolones and linezolid, may be easily switched to oral therapy in such patients (**Level II**) (248, 253, 254).
2. Aerosolized antibiotics have not been proven to have value in the therapy of VAP (**Level I**) (256). However, they may be considered as adjunctive therapy in patients with MDR gram-negatives who are not responding to systemic therapy (**Level III**) (255).
3. Combination therapy should be used if patients are likely to be infected with MDR pathogens (**Level II**) (21, 205). No data have documented the superiority of this approach compared with monotherapy, except to enhance the likelihood of initially appropriate empiric therapy (**Level I**) (262).
4. If patients receive combination therapy with an aminoglycoside-containing regimen, the aminoglycoside can be stopped after 5–7 days in responding patients (**Level III**) (235).
5. Monotherapy with selected agents can be used for patients with severe HAP and VAP in the absence of resistant pathogens (**Level I**) (240, 242–247). Patients in this risk group should initially receive combination therapy until the results of lower respiratory tract cultures are known and confirm that a single agent can be used (**Level II**).
6. If patients receive an initially appropriate antibiotic regimen, efforts should be made to shorten the duration of therapy from the traditional 14 to 21 days to periods as short as 7 days, provided that the etiologic pathogen is not *P. aeruginosa*, and that the patient has a good clinical response with resolution of clinical features of infection (**Level I**) (210).

Specific Antibiotic Regimens

Although initial therapy is empiric, it may be possible on the basis of the recommendations in Tables 3 and 4, modified by knowledge of local microbiologic data, to choose a specific agent when an etiologic pathogen is identified. Recommended empiric therapy and optimal doses appear in Table 5. The choice of specific agents will be dictated by the results of sensitivity testing, the availability of these agents, and issues of cost and formulary restriction. Four MDR pathogens merit special discussion.

Pseudomonas aeruginosa. *P. aeruginosa* has the capacity to readily develop resistance to all known classes of antibiotics, and resistance can develop in 30–50% of patients currently receiving monotherapy, but no data show that this problem can be avoided by the use of combination therapy (240, 261). Cross-infection is also a serious problem and the antibiotics given to adjacent patients may affect the risk for infection with an antibiotic-resistant strain. As mentioned, the benefits of combination therapy are unclear, with the only data supporting this practice coming from a study of *P. aeruginosa* bacteremia (few of which were due to pneumonia) which showed that patients receiving combination therapy were less likely to die (258). A prospective study of an aminoglycoside added to a carbapenem did not show improved outcome or a difference in the rate of developing resistance during therapy, when compared with monotherapy with a carbapenem (261). In another prospective trial, combination therapy with a β-lactam and twice-daily aminoglycosides demonstrated an unacceptable 39% success rate for patients with VAP due to *P. aeruginosa* (263). A metaanalysis evaluating the addition of an aminoglycoside to β-lactam monotherapy showed no benefit for treatment of *P. aeruginosa* in patients with sepsis (262).

All the studies of combination therapy have used an aminoglycoside with a β-lactam, but none have used single daily dosing of the aminoglycoside, nor have they used the maximal effective dose. Whereas a quinolone could be an alternative to an aminoglycoside, with the theoretic advantage of improved respiratory tract penetration, no prospective study has compared a fluoroquinolone-based combination therapy with β-lactam monotherapy. If a quinolone is used in combination therapy for *P. aeruginosa*, ciprofloxacin or levofloxacin may be used on the basis of *in vitro* activity, but should be used only if local susceptibility data show activity of these agents. This remains a problem, because a significant fall in *P. aeruginosa* sensitivity to quinolones resulted with widespread use of these agents in hospital (264, 265). In these reports, levofloxacin had been used at a dosage of 500 mg/day and the impact of using higher dosages (750 mg daily) on resistance patterns is unknown (243). As mentioned, some anecdotal experience has suggested a value of aerosolized antibiotics as an adjunct to systemic therapy in patients with highly resistant *P. aeruginosa* pneumonia (255).

Acinetobacter *species.* The antibiotic armamentarium for treatment of *Acinetobacter* is limited because of native resistance to many classes of antibiotics. The most consistently effective antibiotics are the carbapenems, the sulbactam component of ampicillin–sulbactam, and the polymyxins. Although no randomized trial has been performed, a case series publication has demonstrated equivalent rates of clinical cure in a trauma surgery population with ampicillin–sulbactam compared with imipenem, including patients with imipenem-resistant isolates (56). The emergence of carbapenem-resistant clones suggests that optimal doses of carbapenems should be used. The significant nephrotoxicity of the polymyxins limits widespread intravenous use, but there are reports of efficacy with acceptable toxicity, and these agents can also be used as aerosolized therapy (255, 266). Susceptibility to aminoglycosides is variable and penetration may limit the delivery of adequate tissue levels of antibiotics, suggesting a possible role for aerosol delivery of these agents for selected patients with *Acinetobacter* pneumonia. One report has documented the efficacy and safety of colistin in patients with *Acinetobacter* VAP that was not susceptible to carbapenems (266). Colistin therapy led to a clinical cure in 57% of patients, and none had prolonged neuromuscular blockade as a side effect of therapy.

Extended spectrum β-lactamase–producing **Enterobacteriaceae.** The hallmark of ESBL-producing Enterobacteriaceae is a variable response to cephalosporins and thus third-generation agents should be avoided as monotherapy when these pathogens are suspected or isolated (267). In particular, a third-generation cephalosporin should not be used for *Enterobacter* species because of the documented high frequency of resistance developing on therapy (260). Use of the fourth-generation cephalosporin cefepime for this infection is controversial and the safety of using cefepime in patients previously exposed to third-generation cephalosporins is not well documented (267, 268). A reliable choice is a carbapenem, which is generally active against these organisms (269). Because these microorganisms are also likely to demonstrate resistance to aminoglycosides and fluoroquinolones, the benefit of combination therapy is uncertain. Piperacillin–tazobactam has been used for the treatment of VAP, but the its efficacy against $ESBL^+$ organisms is uncertain and should be used with caution and at adequate doses (Table 5) (270). In a prospective analysis of in-hospital mortality associated with VAP, Fowler and coworkers found that use of an antipseudomonal penicillin with a β-lactamase inhibitor for VAP was associated with a lower risk of death (hazard ratio, 0.41; 95% confidence interval, 0.21–0.80; $p = 0.009$) than when other antibiotics were used (259).

Methicillin-resistant **Staphylococcus aureus.** Although vancomycin has been the accepted standard of therapy for this pathogen, both industry-sponsored clinical trials and studies from individual centers have consistently reported clinical failure rates of 40% or greater with a standard dose (1 g every 12 hours) of vancomycin for MRSA pneumonia (271–273). Combination therapy with other agents, such as rifampin (274), aminoglycosides, and others, has been tried but no prospective clinical data have documented the value of this approach. Retrospective pharmacokinetic modeling has suggested that the vancomycin failures may be related to inadequate dosing (272). Many physicians have therefore tried to achieve a trough concentration 15 mg/L or more, but no prospective clinical data have shown the value of this practice. The use of continuous vancomycin infusions has not been shown to be clearly advantageous compared with twice-daily dosing (275).

Two new agents for serious gram-positive infections have been studied in patients with MRSA pneumonia. A prospective randomized trial of quinupristin–dalfopristin for gram-positive nosocomial pneumonia found worse clinical success rates than with vancomycin for MRSA HAP (271). In contrast, two large multicenter trials of linezolid demonstrated equivalence to vancomycin in patients with HAP (241, 276). When the two studies were combined and analyzed by multivariate techniques, linezolid was found to have a significant association with both clinical cure and lower mortality, especially for patients with VAP due to MRSA (241). This advantage may be due to the higher penetration of linezolid into the epithelial lining fluid than with vancomycin (248, 277). However, optimal dosing of vancomycin may not have been achieved in all patients, and prospective confirmation of these results is needed.

Although the superiority of linezolid over vancomycin for VAP due to MRSA still needs further validation, linezolid may be preferred in several clinical settings. In patients at risk for, or already with, renal insufficiency, physicians have a strong tendency to underdose vancomycin, Dosing vancomycin in patients with fluctuating renal function is difficult and requires frequent monitoring of levels. The presence of renal insufficiency was a significant predictor of vancomycin failure in a multivariate analysis of patients with VAP (241). A related concern is an increased risk of nephrotoxicity in patients with MRSA pneumonia who are receiving vancomycin along with other nephrotoxic medications, particularly aminoglycosides (275, 278, 279).

Antibiotic Heterogeneity and Antibiotic Cycling

Antibiotic cycling or rotation has been advocated as a potential strategy for reducing the emergence of antimicrobial resistance (280). In theory, a class of antibiotics or a specific antibiotic is withdrawn from use for a defined time period and reintroduced at a later point in time in an attempt to limit bacterial resistance to the cycled antimicrobial agents.

When outbreaks of infection with a specific strain of resistant bacteria have occurred, restricted access to specific antibiotics has successfully managed the problem, with generally no impact on the overall frequency of resistance (281). However, if disproportionate use of another antibiotic results, resistance rates may be affected. Rahal and coworkers restricted use of third-generation cephalosporins to combat an outbreak of $ESBL^+$ *Klebsiella* infections (281). Restriction of cephalosporins was accompanied by a 44% reduction in infection and colonization with the $ESBL^+$ *Klebsiella*. However, the use of imipenem increased by 140% during the intervention year and was associated with a 69% increase in the incidence of imipenem-resistant *P. aeruginosa* throughout the medical center. The clinical benefit of shifting resistance from one pathogen to another was uncertain.

Gerding and colleagues evaluated cycling of aminoglycosides over 10 years at the Minneapolis Veterans Affairs Medical Center, cycling amikacin and gentamicin (282). Using cycle times of 12 to 51 months, these investigators found significantly reduced resistance to gentamicin when amikacin was used. Return of resistance with the rapid reintroduction of gentamicin occurred whereas subsequent, more gradual reintroduction of gentamicin occurred without increased levels of resistance. This experience suggests that cycling of antibiotics within the same drug class, in some circumstances, could be an effective strategy for curbing antimicrobial resistance.

Kollef and coworkers examined the influence of a scheduled change in the preferred antibiotic for empiric therapy of infection on the incidence of nosocomial infections in a cardiac surgical ICU (283). A 6-month-before period, during which the traditional practice was to use ceftazidime for the empiric treatment of gram-negative bacterial infections, was followed by a 6-month-after period, during which ciprofloxacin was substituted. Unexpectedly, the overall incidence of VAP was significantly reduced in the after period, primarily as the result of a significant reduction in the incidence of VAP attributed to antibiotic-resistant gram-negative bacteria. Similarly, a lower incidence of antibiotic-resistant gram-negative bacteremia was also observed in the after period. This experience was followed by a series of scheduled antibiotic changes for the treatment of suspected gram-negative bacterial infections among patients admitted to the medical and surgical ICUs (284). The consequence of this policy was an overall improvement in the prescription of appropriate antimicrobial therapy as MDR infections decreased.

Gruson and colleagues observed a reduction in the incidence of VAP after introducing an antimicrobial program that consisted of supervised rotation and restricted use of ceftazidime and ciprofloxacin (235). The antibiotic selection was based on monthly reviews of the pathogens isolated from the intensive care unit and their antibiotic susceptibility patterns. They observed a decrease in the incidence of VAP, primarily because of a reduction in the number of episodes attributed to antibiotic-resistant gram-negative bacteria including *P. aeruginosa*, *B. cepacia*, *S. maltophilia*, and *Acinetobacter baumannii*. Their initial results could be sustained over a 5-year time period (285).

Major points and recommendations for selected MDR pathogens.

1. If *P. aeruginosa* pneumonia is documented, combination therapy is recommended. The principal justification is the high frequency of development of resistance on monotherapy (240). Although combination therapy will not necessarily prevent the development of resistance, combination therapy is more likely to avoid inappropriate and ineffective treatment of patients (**Level II**) (205).
2. If *Acinetobacter* species are documented to be present, the most active agents are the carbapenems, sulbactam, colistin, and polymyxin. There are no data documenting an improved outcome if these organisms are treated with a combination regimen (**Level II**) (56, 266).
3. If $ESBL^+$ Enterobacteriaceae are isolated, then monotherapy with a third-generation cephalosporin should be avoided. The most active agents are the carbapenems (**Level II**) (267).
4. Adjunctive therapy with an inhaled aminoglycoside or polymyxin for MDR gram-negative pneumonia should be considered, especially in patients who are not improving with systemic therapy (**Level III**) (255). More studies of this type of therapy are needed.
5. Linezolid is an alternative to vancomycin for the treatment of MRSA VAP and may be preferred on the basis of a subset analysis of two prospective randomized trials (**Level II**) (241, 276, 286). This agent may also be preferred if patients have renal insufficiency or are receiving other nephrotoxic agents, but more data are needed (**Level III**).
6. Antibiotic restriction can limit epidemics of infection with specific resistant pathogens. Heterogeneity of antibiotic prescriptions, including formal antibiotic cycling, may be able to reduce the overall frequency of antibiotic resistance. However, the long-term impact of this practice is unknown (**Level II**) (284, 285).

RESPONSE TO THERAPY

Modification of Empiric Antibiotic Regimens

Empiric antibiotics may need modification once the results of blood or respiratory tract cultures become available (Figure 1). Modification may be necessary if a resistant or unsuspected pathogen is found in a nonresponding patient. Alternatively, therapy can be deescalated or narrowed if an anticipated organism (such as *P. aeruginosa* or an *Acinetobacter* species) was not recovered or if the organism isolated is sensitive to a less broad-spectrum antibiotic than was used in the initial 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, little information about the natural course of HAP resolution is available. In addition, because of the unreliability 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 the 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 (287). Using this approach, clinical improvement usually becomes apparent after the first 48–72 hours of therapy and, therefore, the selected antimicrobial regimen should not be changed during this time unless progressive deterioration is noted or initial microbiologic studies so dictate (208, 287).

Appropriate respiratory tract cultures can be used to define microbiologic resolution. Using serial cultures, end points can be defined, such as bacterial eradication, superinfections (infection with a new organism), recurrent infection (elimination, then return, of original organism), or microbiologic persistence. Serial quantitative microbiologic studies of lower respiratory tract secretions can also define resolution end points (193). In one such study, repeat PSB samples collected 72 hours after starting therapy were used to define the bacteriologic response to therapy. The results of these microbiologic evaluations were compared with the clinical outcome (288). When the follow-up PSB sample showed no growth or less than 10^3 cfu/ml, a clinical therapeutic failure occurred only 7% of the time, whereas a finding of greater than 10^3 cfu/ml (microbiologic failure to eradicate) was associated with clinical failure in 55.8% of the patients. At present, use of early recognition of a microbiologic nonresponse to modify therapy has not been prospectively studied.

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 (e.g., chronic obstructive pulmonary disease) (208). However, the finding of a rapidly deteriorating radiographic pattern, with a follow-up chest radiograph showing progression to multilobar involvement, a greater than 50% increase in the size of the infiltrate within 48 hours, development of cavitary disease, or significant pleural effusion, should raise concern (5).

Clinical parameters including the white blood cell count and measures of oxygenation and core temperature have been used in several studies to define the normal pattern of resolution of HAP. Dennesen and coworkers demonstrated that, among patients treated with initial appropriate antibiotic therapy, clinical improvement in these parameters occurred progressively during the first week of antibiotic treatment (193). Little further improvement in fever, white blood cell count, or the Pa_{O_2}/Ft_{O_2} ratio occurred beyond 7 days of antibiotic treatment. Similarly, Luna and coworkers used changes in the CPIS as a measure of resolution or deterioration among patients with VAP, rather than its traditional application as a tool with which to diagnose pneumonia (208). Improvement in the CPIS occurring during the first 3 days of empiric treatment was associated with hospital survival whereas a lack of improvement in the CPIS predicted mortality. Inappropriate antibiotic treatment of VAP was also associated with a lack of clinical improvement in the CPIS, particularly in serial measurements of arterial oxygenation.

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 (Figure 3).

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, whereas any mechanically ventilated patient can have pulmonary hemorrhage (195, 289). In one series, 26 of 69 ventilated patients with new lung infiltrates had pulmonary hemorrhage at autopsy, sometimes in association with pneumonia (195).

Host factors associated with a failure to improve during em-

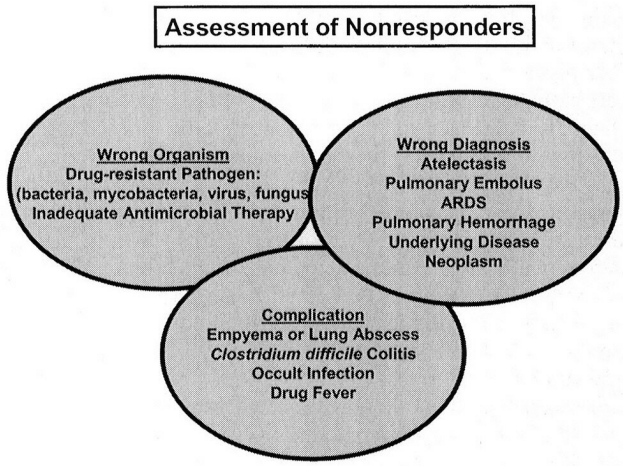

Figure 3. Possible causes for lack of clinical response to initial antibiotic therapy include the wrong organism, the wrong diagnosis, or other complications. ARDS = adult respiratory distress syndrome.

piric therapy include the presence of any condition that is known to increase mortality. These include prolonged mechanical ventilation, respiratory failure, an underlying fatal condition, age greater than 60 years, bilateral radiographic infiltrates, prior antibiotic therapy, prior pneumonia (i.e., the current episode represents superinfection), and/or chronic lung disease (12, 13, 287, 290).

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 antibiotic or can acquire resistance during therapy, particularly *P. aeruginosa* treated with a single agent (240). Some organisms are inherently difficult to eradicate, even with effective therapy (288). In one study of *P. aeruginosa* pneumonia in an ICU, 20 of 34 patients survived an initial episode of infection. However, among the survivors, recurrent infection developed, as defined by clinical, radiographic, and bacteriologic criteria, in 50% (291). 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 (10, 290). In patients who are mechanically ventilated, superinfection with *P. aeruginosa* or *Acinetobacter* species has a particularly high mortality, approaching 90% in some series (292). Finally, pneumonia can be due to other pathogens (i.e., *Mycobacterium tuberculosis*, fungi, or respiratory viruses) or an unusual bacterial pathogen not included in the initial empiric regimen. In addition, some patients can have clinically unrecognized immunosuppression (e.g., acquired immunodeficiency syndrome), and unrecognized *Pneumocystis carinii* pneumonia may be a cause of nonresponse to therapy.

Certain complications during therapy can also lead to an apparent failure in response to therapy. Some patients with HAP can have other sources of fever simultaneously, particularly sinusitis, vascular catheter-related infection, pseudomembranous enterocolitis, or urinary tract infections (109, 293). 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 (Figures 1 and 3), 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 lower respiratory tract secretions for culture and antimicrobial sensitivity patterns. This can be done by collecting an endotracheal aspirate if the patient is intubated, or by a bronchoscopic procedure with quantitative cultures for both intubated and nonintubated patients. Even though patients in this clinical setting are receiving antibiotics, the recovery by invasive methods of organisms at high concentrations is possible and may indicate that infection with a resistant organism is present (192). 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, catheter 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 radiographs, ultrasound, or computerized tomographic scanning may reveal pleural fluid, which should be evaluated to exclude empyema. In addition, computerized tomographic scanning can separate pleural fluid from parenchymal disease and can demonstrate parenchymal abscesses, adenopathy, and pulmonary masses. Computerized tomographic 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 (294). One commonly infected site in patients with nasotracheal or nasogastric tubes in place is the sinuses, and computerized tomographic scanning can identify opacification 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 (109). Evaluation for pulmonary embolus may be needed for selected patients because pulmonary infarction can be confused with pneumonia.

If this microbiologic and radiographic evaluation is negative, a decision should be made concerning whether to observe the patient while either continuing or empirically changing antibiotics or to perform an open lung biopsy to obtain the diagnosis of an unusual pathogen or of a noninfectious illness that mimics pneumonia. There is debate about the value of open lung biopsy in nonimmunosuppressed patients with suspected HAP, VAP, or HCAP. 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 extrapulmonary infectious foci, should be performed 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 evaluations are unrevealing, an alteration in antibiotics or initiation of antiinflammatory therapy (corticosteroids) may be appropriate before proceeding with an open biopsy. However, if the patient deteriorates early (within the first 48–72 hours of therapy) or has initially improved but then deteriorates, additional antibiotics directed at resistant or "unusual" bacteria can be added while doing aggressive radiographic and microbiologic evaluations.

Major Points and Recommendations for Assessing Response to Therapy

1. A serial assessment of clinical parameters should be used to define the response to initial empiric therapy (**Level II**) (193, 208). Modifications of empiric therapy should be made on the basis of this information, in conjunction with microbiologic data (**Level III**).
2. Clinical improvement usually takes 48–72 hours, and thus therapy should not be changed during this time unless there is rapid clinical decline (**Level III**). Nonresponse to therapy is usually evident by Day 3, using an assessment of clinical parameters (**Level II**) (193, 208).
3. The responding patient should have de-escalation of antibiotics, narrowing therapy to the most focused regimen possible on the basis of culture data (**Level II**) (205).
4. The nonresponding patient should be evaluated for noninfectious mimics of pneumonia, unsuspected or drug-resistant organisms, extrapulmonary sites of infection, and complications of pneumonia and its therapy. Diagnostic testing should be directed to whichever of these causes is likely (**Level III**) (293).

SUGGESTED PERFORMANCE INDICATORS

1. Circulate HAP guidelines to appropriate medical staff (administrators for quality and safety, physicians, and nurses) for review.
2. Provide epidemiologic data on the prevalence and types of MDR pathogens in intensive care unit patients and current antibiograms, to select appropriate initial antibiotic therapy.
3. Select specific parts of the guideline for implementation by the medical and surgical services, including the intensive care units, and monitor compliance with the guidelines in relation to patient outcomes from HAP.
4. Identify modifiable risk factors for HAP, and develop programs to reduce the risk of pneumonia through changing these risk factors.

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Conflict of Interest Statement: M.J.B. received $5,000 for consultancy from Intrabiotics Pharmaceuticals, Inc. in 2003–2004, and his department received an unrestricted research grant of $30,000 from this company in 2003; J.C. received $14,000 in 2003–2004 for serving on an Advisory Board for Intrabiotics and has participated as a speaker in scientific meetings or courses organized and financed by various pharmaceutical companies (Pfizer, Wyeth, Brahms); W.A.C. received in 2001–2004 advisory committees/consultation fees of $5,500 from Bristol-Myers Squibb, $4,500 from Cubist Pharmaceuticals, $3,500 from GlaxoSmithKline, $3,000 from Bayer, $2,500 from Wyeth, and $2,000 from Pfizer/Pharmacia, and received research grants of $137,200 from GlaxoSmithKline, $108,000 from Sanofi-Aventis, $39,000 from Wyeth and $35,000 from Bayer; D.E.C. has received less than $3,000 per year for participating in the speaker's bureaus for Cubist, Merck, Elan, and Pfizer; J.-Y.F. has participated as a speaker in scientific meetings organized and financed by Pfizer and served on Advisory Boards for Intrabiotics and Wyeth; J.H. has served on Advisory Boards for Bayer, Lilly, Elan, and Pharmacia and has received less than $10,000 in speaker fees over the last three years for activities supported by Bayer, Pharmacia, and Ortho-Biotech; G.A.J. has received consultation or lecture fees from Bayer and Ortho-McNeil and grant support from Merck; M.H.K. has received honoraria for lectures from Pfizer, Elan, Bayer, Pharmacia, and Merck and has received an industry-sponsored research grant from Elan and has also served on the Advisory Boards of Pfizer, Elan, and Bayer; C.M.L. has received unrestricted and restricted research support and has participated as a speaker in scientific meetings or courses organized and/or financed by various pharmaceutical companies (Merck, Bayer, Pfizer, Bristol-Myers Squibb, Astra Zeneca, Aventis) and received $10,000 in 2003 and 2004 from AstraZeneca for participating in a multicenter clinical trial; L.A.M. received less than $10,000 over the last three years from Bayer, Pfizer, Oscient, Wyeth for advisory boards and speaker's bureaus and over $10,000 from Pfizer for speaker's bureau over the last three years and over $10,000 for research from Bayer, Pfizer, Ortho-McNeil, Aventis over the last three years; M.S.N. has served as a consultant or advisor over the past three years to Merck, Elan, Chiron, Pfizer, Bayer, AstraZeneca, and Wyeth-Ayerst and has also served as a lecturer over the past three years for Merck, Elan, Chiron, Pfizer, Bayer, AstraZeneca, Ortho-McNeil, and Wyeth-Ayerst and has also received research funding from Aerogen Pharmaceuticals and Bard Medical and has been a consultant for Aerogen in 2003 and 2004; A.T. received €900 for a conference given in a mini-symposium sponsored by GlaxoSmithKline, and in addition has participated on international Advisory Boards of Abbott (€2500), Aventis (€2000) and Bayer (€900) in the years 2003 and 2004; R.G.W. has received an Investigator-initiated research grant from Eli Lilly and Co. for $90,000 in 2003 and is a paid consultant to Pfizer Inc. (previously Pharmacia) and is on their speaker's bureau and has received approximately $6,000/year for the last three years and is a consultant to Mpex Pharmaceuticals, Peninsula Pharmaceuticals, Bayer, and Chiron Inc. and has spoken at scientific meetings and courses organized by Ortho-McNeil, WyethAyerst, and AstraZeneca.

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