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Chapter 43

Pneumonia: Considerations for the Critically Ill Patient

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Pneumonia is the sixth leading cause of death in the United States and the number one cause of death from infectious diseases. The patient with pneumonia is managed in the intensive care unit (ICU) when severe forms of community-acquired pneumonia (CAP) are present or when a hospitalized patient develops a life-threatening nosocomial pneumonia (NP). A newly defined entity, health care–associated pneumonia (HCAP), is a form of NP that arises in patients who have been in contact with environments such as nursing homes and hemodialysis centers that expose them to the multidrug-resistant bacteria present in the hospital; these patients frequently develop severe pneumonia.[1,2] In the ICU almost 90% of episodes of NP occur in patients who are being mechanically ventilated for other reasons, and this is termed *ventilator-associated pneumonia* (VAP). The elderly account for a disproportionate number of critically ill patients with all forms of pneumonia, often because they commonly have comorbid illness that predisposes them to more severe forms of infection, and their short- and long-term mortality is higher than that of younger patients.[3] In all forms of severe pneumonia, antibiotic resistance is an increasing problem, especially among pneumococci in CAP, and with *Pseudomonas aeruginosa*, *Acinetobacter* spp., extended-spectrum β-lactamase–producing gram-negatives, and methicillin-resistant *Staphylococcus aureus* (MRSA) in VAP and HCAP.[1,2] Although patients with HIV infection and those with other immunocompromising diseases commonly develop pneumonia, the approach to managing these patients is very specific and different from that used in immunocompetent patients. Therefore these populations are not discussed here.

Pneumonia is unusual among medical illnesses because its pathogenesis, therapy, and prevention can be discussed, but there is tremendous controversy about how to best diagnose its presence. Although the clinical definition requires the presence of a new radiographic infiltrate and supporting clinical information for the presence of infection, the diagnosis of ventilator-associated pneumonia is imprecise, and most physicians are relegated to managing patients from this imperfect perspective. Considerable controversy exists about whether a more precise and accurate bacteriologic definition of pneumonia would lead to improved patient outcome, with some recent studies focusing on this issue.[2,4,5] Numerous other controversies related to pneumonia therapy and prevention are also debated among critical care physicians and are discussed in this chapter.

DEFINITIONS OF SEVERE PNEUMONIA, RISK FACTORS, AND PROGNOSIS

Among patients with CAP admitted to the hospital, 10% to 20% require care in the ICU and the rates are higher in elderly patients.[6,7] No uniform definition of severe pneumonia exists, but patients who need ICU care are often those with either respiratory failure (hypoxemic or hypercarbic) requiring mechanical ventilation or noninvasive ventilation; septic shock; or other clinical features of serious illness such as respiratory rate greater than 30 breaths per minute, systolic blood pressure (BP) less than 90 mm Hg or diastolic BP less than 60 mm Hg, multilobar infiltrates, Pa_{O_2}/F_{IO_2} ratio less than 250, confusion, or

destabilization of another serious medical problem.[1,8] In patients with severe CAP, the expected mortality rate for those admitted to the ICU is 35% to 40%, but higher rates have been observed if the majority of ICU-admitted patients are mechanically ventilated, implying that the prognosis is worse if ICU care is first provided late in the course of illness.[9] One recent study found that CAP accounted for 5.9% of all ICU admissions in the United Kingdom and that 59% were admitted within the first 2 days of hospital stay. In this group, 55% were mechanically ventilated on ICU entry and the mortality rate was lowest (46%) in those admitted within the first 2 days, compared with those admitted later in the course of hospital illness.[9] On the basis of a number of studies, a reasonable benchmark is that approximately 60% of all ICU CAP patients will be mechanically ventilated at the time of admission.[6,7,10]

Among those with VAP, mortality rates can be as high as 50% to 70%, and case-control studies have documented mortality directly attributable to the presence of pneumonia.[11] Antibiotic-resistant organisms may add to the mortality rate of VAP, not because of increased virulence but rather because these organisms are often not anticipated and, when present, are often initially treated with ineffective antibiotic regimens.[12] HCAP is a form of NP that includes patients with pneumonia developing any time during their hospital stay (including on admission) who have been exposed to the drug-resistant bacteria present in the health care environment. This includes any patient with a history of hospitalization in the past 3 months, admission from a long-term care facility, need for dialysis or home infusion therapy, home wound care, or antibiotic therapy in the past 3 months.[2,13]

A number of studies have defined the risk factors for severe forms of CAP and VAP, as well as the clinical parameters associated with an increased risk for patient mortality.

Risk Factors for Severe Forms of Community-Acquired Pneumonia

Most patients with severe CAP (45% to 65%) have coexisting illnesses, and patients who are chronically ill have an increased likelihood of developing a complicated pneumonic illness (Box 43-1).[1,14] The most common chronic illnesses in these patients are respiratory diseases such as chronic obstructive lung disease (COPD), cardiovascular disease, and diabetes mellitus. In addition, certain habits such as cigarette smoking and alcohol abuse are also quite common in those with severe CAP, and cigarette smoking has been identified as a risk factor for bacteremic pneumococcal infection.[15] Other common illnesses in those with CAP include malignancy and neurologic illness (including seizures). Milder forms of pneumonia may be more severe on presentation if patients have not received antibiotic therapy prior to hospital admission. In addition, genetic differences in the immune response may predispose certain individuals to more severe forms of infection and adverse outcomes and may be reflected by a family history of severe pneumonia or adverse outcomes from infection.[16]

Box 43-1

Risk Factors for Developing Severe Community-Acquired Pneumonia

- Advanced age (older than 65)
- Comorbid illness
- Chronic respiratory illness (including COPD), cardiovascular disease, diabetes mellitus, neurologic illness, renal insufficiency, malignancy
- Cigarette smoking (risk for pneumococcal bacteremia)
- Alcohol abuse
- Absence of antibiotic therapy prior to hospitalization
- Failure to contain infection to its initial site of entry
- Immune suppression
- Genetic polymorphisms in the immune response

Risk Factors for Mortality from Community-Acquired Pneumonia

In a meta-analysis of 33,148 patients with CAP, the overall mortality rate was 13.7%, but those admitted to the ICU had a mortality rate of 36.5%.[17] Eleven prognostic factors were significantly associated with different odds ratios (ORs) for mortality: male sex (OR = 1.3), pleuritic chest pain (OR = 0.5), hypothermia (OR = 5.0), systolic hypotension (OR = 4.8), tachypnea (OR = 2.9), diabetes mellitus (OR = 1.3), neoplastic disease (OR = 2.8), neurologic disease (OR = 4.6), bacteremia (OR = 2.8), leukopenia (OR = 2.5), and multilobar infiltrates (OR = 3.1). In other studies the clinical features that predict a poor outcome (Box 43-2) include advanced age (older than 65 years), preexisting chronic illness of any type, the absence of fever on admission, respiratory rate greater than 30 breaths per minute, diastolic or systolic hypotension, elevated blood urea nitrogen (BUN) (>19.6 mg/dL), profound leukopenia or leukocytosis, inadequate antibiotic therapy, need for mechanical ventilation, hypoalbuminemia, and the presence of certain "high-risk" organisms (type III pneumococcus, *S. aureus*, gram-negative bacilli, aspiration organisms, or postobstructive pneumonia). Other studies have found that when CAP patients have a delay in the initiation of appropriate antibiotic therapy of more than 4 hours, mortality is increased.[18-20]

Prognostic scoring approaches have been applied to predict mortality in CAP patients, and two prominent systems are the pneumonia severity index (PSI) and a modification of the British Thoracic Society rule, referred to as *CURB-65*.[8,21-23] The PSI is a complex scoring system that places patients into one of five risk groups for death on the basis of age, presence of male sex, comorbid illness, and certain laboratory and physical findings. This tool is good for predicting mortality, but it heavily weights age and comorbidity and does not account for the social needs of patients, so it may not help to define the optimal site of care for a given patient. The CURB-65 approach assesses the presence of confusion, elevated

Box 43-2

Risk Factors for a Poor Outcome from Community-Acquired Pneumonia

Patient-Related Factors
Male sex
Absence of pleuritic chest pain
Nonclassic clinical presentation (nonrespiratory presentation)
Neoplastic illness
Neurologic illness
Age older than 65 years
Family history of severe pneumonia or death from sepsis

Abnormal Physical Findings
Respiratory rate greater than 30 breaths per minute on admission
Systolic (<90 mm Hg) or diastolic (<60 mm Hg) hypotension
Tachycardia (>125 beats/min)
High fever (>40°C) or afebrile
Confusion

Laboratory Abnormalities
BUN >19.6 mg/dL
Leukocytosis or leukopenia
Multilobar radiographic abnormalities
Rapidly progressive radiographic abnormalities during therapy
Bacteremia
Hyponatremia (<130 mmol/L)
Multiple organ failure
Respiratory failure
Hypoalbuminemia
Arterial pH <7.35
Pleural effusion

Pathogen-Related Factors
High-risk organisms
Type III pneumococcus, *Staphylococcus aureus*, gram-negative bacilli (including *Pseudomonas aeruginosa*), aspiration organisms, severe acute respiratory syndrome
Possibly high levels of penicillin resistance (minimum inhibitory concentration of at least 4 mg/L) in pneumococcus

Therapy-Related Factors
Delay in initial antibiotic therapy (more than 4 to 6 hours)
Initial therapy with inappropriate antibiotic therapy
Failure to have a clinical response to empiric therapy within 72 hours

BUN, respiratory rate greater than 30 breaths per minute, low blood pressure (either systolic <90 mm Hg or diastolic <60 mm Hg), and whether the patient is at least 65 years old. If 3 of these 5 criteria are present, the predicted mortality rate is greater than 20%.[22,23]

Prognostic scoring systems have been used to define the need for ICU admission, with the suggestion that ICU care be considered for those in PSI classes IV and V or those with a CURB-65 score of 3 or higher.[8,23] This may not always be effective because up to 37% of those admitted to the ICU are in PSI classes I to III, and risk for death (which PSI can measure) is not always the same as need for intensive care.[8] Conversely, patients in higher PSI classes do not always need ICU care if they fall into these high-mortality-risk groups because of advanced age and comorbid illness, in the absence of physiologic findings of severe pneumonia. Neither of the current prognostic scoring systems is ideal by itself for defining the need for ICU care, and both can be regarded only as providing decision support information that must be supplemented by clinical assessment and judgment. In addition, the two scoring approaches should be viewed as being complementary to one another.[24] For example, in one recent study that compared the PSI with the CURB-65, both were good for predicting mortality and in identifying low-mortality-risk patients. However, the CURB-65 appeared to be more discriminating in defining mortality risk in the severely ill.[23] In another study, Ewig and colleagues[25] examined the 10 criteria in the 1993 American Thoracic Society guidelines to define severe CAP. They found that need for ICU was defined by the presence of two of three minor criteria (systolic BP <90, multilobar disease, PaO_2/FIO_2 ratio <250) or one of two major criteria (need for mechanical ventilation or septic shock).[25] On the basis of these observations, the 2001 ATS guidelines for CAP recommend that severe CAP could be defined on the basis of the presence of these features.[1]

Other investigators have shown that the use of early and effective empiric therapy can improve survival in the setting of severe CAP. Retrospective data have shown a reduced mortality for admitted CAP patients who are treated within 4 hours of arrival to the hospital, compared with those who are treated later.[18] Ineffective initial empiric therapy was a potent predictor of death, being associated with a 60% mortality rate, compared with an 11% mortality rate for those who received initial effective therapy.[10] Similarly, in other studies of CAP, the combined use of a β-lactam and a macrolide antibiotic was associated with a lower mortality than if other therapies were given.[26,27]

Among patients with severe CAP, another important prognostic finding is clinical evolution, as reflected by radiographic progression during therapy.[6] The elderly with CAP often have a higher risk of dying than other populations, in part because adverse prognostic features are particularly common in this population.[3] In one series the mortality rate of nursing home–acquired pneumonia was 32%, compared with a mortality rate of 14% in other patients with CAP.[28] One factor that may explain this finding is that older patients often have atypical clinical presentations of pneumonia, which may lead to their being diagnosed at a later, more advanced stage of illness, resulting in an increased risk of death.[29] In part, as a consequence of these unusual clinical presentations, when these patients come to the hospital for evaluation, there

are often delays in establishing the correct diagnosis. This leads to delays in initiating timely therapy and further increases the risk of dying.[20] Older patients from nursing homes who present with pneumonia are now included in a separate category, HCAP (discussed earlier).

Risk Factors for Ventilator-Associated Pneumonia

Mechanical ventilation for more than 2 days is the most important risk factor for NP, but other identified risks include being older than 60 years of age, malnutrition (serum albumin <2.2 g/dL), acute lung injury (acute respiratory distress syndrome [ARDS]), coma, burns, recent abdominal or thoracic surgery, multiple organ failure, transfusion of greater than 4 units of blood, transport from the ICU, prior antibiotic therapy, elevation of gastric pH (by antacids or histamine–type 2 blocking agents), large-volume aspiration, use of a nasogastric tube (rather than a tube placed in the jejunum or a tube inserted through the mouth), use of inadequate endotracheal tube cuff pressure, prolonged sedation and paralysis, maintaining patients in the supine position in bed, use of total parenteral nutrition feeding rather than enteral feeding, and repeated reintubation.[2] When a patient is mechanically ventilated, the risk of pneumonia is greatest in the first 5 days (3% per day). It declines thereafter to a risk of 2% per day for days 6 to 10 and to a rate of 1% per day or lower after this.[30] Noninvasive ventilation for respiratory failure is associated with a much lower risk of pneumonia than endotracheal intubation.

The relation between pneumonia and ARDS is particularly interesting. As many as one third of all cases of ARDS may be the result of pneumonia, and in some series pneumonia is the most common cause of acute lung injury. Not only can a variety of CAPs serve as a cause of ARDS, but secondary NP is the most common infection acquired by patients with established ARDS.[31-33] However, it has been shown that when patients with ARDS develop pneumonia, it is generally a late event, occurring after at least 7 days of mechanical ventilation.[32]

Pneumonia also presents a particular problem in the postoperative patient, particularly after elective thoracic, cardiac, or abdominal surgery. Other surgical groups that are at high risk for pneumonia include the victims of major trauma, particularly those suffering head injury and blunt chest trauma. When a patient has a pulmonary contusion, it may be difficult to distinguish this process from secondary lung infection on the basis of clinical and radiographic findings.

Risk Factors for Mortality from Ventilator-Associated Pneumonia

The factors associated with the greatest impact on attributable mortality are the accuracy and timeliness of initial antibiotic therapy. Use of the wrong therapy or delays in the initiation of therapy are the most important predictors of VAP mortality.[11,12,34] Initial appropriate therapy (using an agent to which the etiologic pathogen is sensitive) can reduce mortality, but administration of correct therapy at a later date, after initially incorrect therapy, may not effectively reduce mortality.[34] The benefit of accurate empiric therapy may not apply to all patients, but may be greatest for those infected with *P. aeruginosa* or *S. aureus*[35] and for those without the most severe degree of multiple organ dysfunction at the time of therapy.[36] For some patients, even using the correct therapy does not reduce mortality if it is not given in adequate doses and if the therapy does not reach the site of infection.

Closely related to appropriateness of initial therapy is the ability to decrease the number and/or spectrum of antimicrobial therapy once culture data become available, referred to as "de-escalation." Several recent studies have demonstrated that the use of de-escalation is associated with lower mortality compared with escalation or compared with a strategy of making no effort to reduce antibiotic therapy.[37,38] The choice of how to administer a specific agent can also affect outcome, and one study of MRSA VAP found that the mortality with intermittent infusion of vancomycin was twice as high as when this agent was administered by continuous infusion.[39] Other risk factors for mortality include prolonged duration of ventilation, coma on admission, creatinine greater than 1.5, transfer from another ward to the ICU, the presence of certain "high-risk" pathogens (particularly an antibiotic-resistant organism such as *P. aeruginosa*, *Acinetobacter* spp., or *S. aureus)*, bilateral radiographic abnormalities, age older than 60 years, an ultimately fatal underlying condition, shock, prior antibiotic therapy, multiple-system organ failure, nonsurgical primary diagnosis, or a rising APACHE score during pneumonia therapy (Box 43-3).[2,40]

Box 43-3

Risk Factors for Mortality from Nosocomial Pneumonia

Physiologic Findings
Respiratory failure
Coma on admission
Multiple system organ failure
Acute physiology and chronic health evaluation II score rising to greater than 20 at 72 hours after diagnosis

Laboratory Findings
Creatinine >1.5 mg/dL
Gram-negative pneumonia, especially *Pseudomonas aeruginosa.* or *Acinetobacter* infection
Infection with any drug-resistant pathogen
Bilateral radiographic abnormalities
Fungal pneumonia
Polymicrobial infection

Historical Data
Prior antibiotic therapy
Age older than 60 years
Underlying fatal illness
Prolonged mechanical ventilation
Inappropriate antimicrobial therapy
Transfer to the intensive care unit from another ward

Although a number of host and bacteriologic factors enhance the mortality risk of NP, developing a superinfection, as opposed to a primary NP, is a particularly ominous finding. Rello observed that pulmonary superinfection had a 67% mortality, whereas primary NP had a 38% mortality rate.[41] In earlier studies, Graybill[42] observed a 62% mortality rate with superinfection pneumonia, compared with a 40% mortality rate for primary nosocomial lung infection. These data, as well as information from Fagon and colleagues[43] and Trouillet and colleagues,[44] emphasize the important role of prior antibiotics in enhancing mortality, an outcome that is likely the result of secondary infection by more virulent pathogens. As a result, antibiotic use has two pivotal roles in prognosticating outcome from NP: outcome is improved if the correct therapy is chosen, but if this therapy is followed by superinfection, then mortality is much more likely, generally because these infections involve difficult-to-treat, drug-resistant organisms.

PATHOGENESIS

General Overview

Pneumonia results when host defenses are overwhelmed by an infectious pathogen. This may occur because the patient has an inadequate immune response, often as the result of underlying comorbid illness; because of anatomic abnormalities (endobronchial obstruction, bronchiectasis); or because of therapy-induced dysfunction of the immune system (corticosteroids, endotracheal intubation).[2,45,46] In addition, genetic variations in the immune response make some patients prone to overwhelming infection because of an inadequate response and others prone to acute lung injury because of an excessive immune response.[16] In fact, the failure to localize the immune response to the respiratory site of initial infection may explain why some patients develop acute lung injury and sepsis because the inflammatory response extends to the entire lung and systemic circulation.[47] Pneumonia can even occur in patients who have an adequate immune system, if the host defense system is overwhelmed by a large inoculum of bacteria (massive aspiration) or by a particularly virulent organism to which the patient has no preexisting immunity or to which the patient has an inability to form an adequate immune response. With this paradigm in mind, it is easy to understand why previously healthy individuals develop infection with virulent pathogens such as viruses (influenza), *Legionella pneumophila*, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Streptococcus pneumoniae*. However, for chronically ill patients, it is possible for them to be infected not by these virulent organisms but also by organisms that are not highly virulent. Because of host defense impairments, organisms that commonly colonize these patients can cause infection as a result of immune responses that are inadequate. These organisms include enteric gram-negative bacteria (*Escherichia coli*, *Klebsiella pneumoniae*, *P. aeruginosa*, *Acinetobacter* spp.) and fungi (*Aspergillus* and *Candida* spp.).

Bacteria can enter the lung via several routes, but aspiration from a previously colonized oropharynx is the most common way that patients develop pneumonia. Although most pneumonias result from micro-aspiration, patients can also aspirate large volumes of bacteria if they have impaired neurologic protection of the upper airway (stroke, seizure) or gastrointestinal illnesses that predispose to vomiting. Other routes of entry include inhalation, which applies primarily to viruses, *Legionella pneumophila* and *Mycobacterium tuberculosis*; hematogenous dissemination from extra-pulmonary sites of infection (right-sided endocarditis); and direct extension from contiguous sites of infection. In critically ill hospitalized patients, bacteria can also enter the lung from a colonized stomach (spreading retrograde to the oropharynx, followed by aspiration), a colonized or infected maxillary sinus, and colonization of dental plaque, or they can enter the lung directly via the endotracheal tube (from the hands of staff members). Recent studies have shown that the use of nasal tubes (into the stomach or trachea) can predispose to sinusitis and pneumonia, but that a gastric source of pneumonia pathogens in ventilated patients is not common.[48,49]

Role of Respiratory Therapy Equipment and Endotracheal Tubes

The endotracheal tube bypasses the filtration and host defense functions of the upper airway and can act as a conduit for direct inoculation of bacteria into the lung. This route may be particularly important if bacteria colonize the inside of the endotracheal tube itself.[50,51] This can occur if tracheobronchial organisms reach the endotracheal tube, a site where they are able to proliferate free from any impediment by the host defense system. Bacteria commonly grow at this location in a biofilm, which promotes the growth of multidrug-resistant organisms.[51] The biofilm represents a "sequestered nidus" of infection on the inside of the endotracheal tube, and particles can be dislodged every time the patient is suctioned. This is one of the mechanisms explaining the strong association between endotracheal intubation and pneumonia. Given the presence of biofilm in endotracheal tubes, it may be tempting to regularly reintubate patients and use a fresh tube, but this approach is not recommended because reintubation is itself a risk factor for VAP.[52]

Just as a patient's own tracheobronchial flora can spread to the endotracheal tube and amplify to large numbers, a similar phenomenon can occur in respiratory therapy equipment and in ventilator circuits.[53,54] Ventilator circuit colonization studies indicate that the greatest numbers are found at sites closest to the patient, not the ventilator, suggesting that circuit contamination originates from the patient.[53] One highly contaminated site is the condensation in the tubing, and this material can inadvertently be inoculated into patients if the tubing is not handled carefully. Because condensate colonization occurs in 80% of tubings within 24 hours, it does not appear that frequent ventilator circuit changes are useful or even able to reduce the risk of pneumonia; in one study, tubing changes every 24 hours (rather than every 48 hours) served as a risk

factor for pneumonia.[55] Although most patients have ventilator tubing changed every 48 hours, several studies have shown no increased risk of infection if tubing is never changed or changed infrequently.[56,57] The use of heat moisture exchangers may be one way to avoid this problem, but they have had an inconsistent effect on preventing VAP. In addition, frequent changes of heat moisture exchangers (i.e., every 24 hours) have not been shown to have an impact on the incidence of VAP, and heat moisture exchangers should be changed no more frequently than every 48 hours.[58]

CLINICAL FEATURES OF PNEUMONIA

Historical Information

Pneumonia is generally characterized by symptoms of fever, cough, purulent sputum production, and dyspnea in a patient with a new or progressive lung infiltrate, with or without an associated pleural effusion. In nonventilated patients, cough is the most common finding. Cough is present in up to 80% of all CAP patients but is less common in those who are elderly, those with serious comorbidity, or individuals coming from nursing homes. Patients with CAP and an intact immune system generally have classic pneumonia symptoms, but the elderly patient can have a nonrespiratory presentation with symptoms of confusion, falling, failure to thrive, altered functional capacity, or deterioration in a preexisting medical illness such as congestive heart failure.[59] The absence of clear-cut respiratory symptoms and an afebrile status have themselves been predictors of an increased risk of death. Pleuritic chest pain is also commonly seen in patients with CAP, and in one study its absence was also identified as a poor prognostic finding.[60]

Certain clinical conditions are associated with specific pathogens in patients with CAP, and these associations should be evaluated when obtaining a history (Table 43-1).[1] For example, if the presentation is subacute, following contact with birds, rats, or rabbits, then the possibility of psittacosis, leptospirosis, tularemia, or plague should be considered. *Coxiella burnetii* (Q fever) is a concern with exposure to parturient cats, cattle, sheep, or goats; *Francisella tularensis* with rabbit exposure; hantavirus with exposure to mice droppings in endemic areas; *C. psittaci* with exposure to turkeys or infected birds; and Legionella with exposure to contaminated water sources (saunas). Following influenza, superinfection with pneumococcus, *S. aureus* including MRSA, and *Hemophilus influenzae* should be considered. With travel to endemic areas in Asia, the onset of respiratory failure after a preceding viral illness should lead to suspicion of a viral

Table 43-1. Likely Microbiologic Etiology and Host Epidemiology of CAP and NP/VAP

Epidemiology	Suspected Pathogen
Community-Acquired	
Alcoholism	Pneumococcus (including drug-resistant organisms), anaerobes, *H. influenzae, K. pneumoniae,* tuberculosis
Splenic dysfunction (sickle cell disease)	Pneumococcus, *H. influenzae*
COPD	Pneumococcus, *H. influenzae, M. catarrhalis*
Recent influenza infection	Pneumococcus, *S. aureus* (including MRSA), *H. influenzae,* enteric gram-negatives
High-risk aspiration	Anaerobes, enteric gram-negative bacilli
Neutropenia (including chronic corticosteroid therapy)	Gram-negative bacilli (esp. *P. aeruginosa*); *Aspergillus*
HIV infection (risk groups: intravenous drug abuser, tuberculosis, hemophilia, homosexual)	Pneumococcus, *H. influenzae, Pneumocystis jerovicii*
Rabbit exposure	*Francisella tularensis*
Exposure to farm animals, parturient cats	*Coxiella burnetii* (Q fever)
Exposure to mouse droppings	Hantavirus
Nursing Home–Acquired (no prior antibiotics and good functional status)	Pneumococcus (including drug-resistant organisms) and other organisms of CAP
Nursing Home–Acquired (prior antibiotics or poor functional status)	Gram-negative bacilli (including *P. aeruginosa, Acinetobacter* spp., ESBL-producing *Enterobacteriaceae*), *S. aureus* (including MRSA)
Hospital-Acquired and VAP	Gram-negative bacilli (including *P. aeruginosa, Acinetobacter* spp., ESBL-producing *Enterobacteriaceae*), *S. aureus* (including MRSA) Consider local microbiology

CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; ESBL, extended-spectrum β-lactamase; MRSA, methicillin-resistant *Staphylococcus aureus;* NP/VAP, nosocomial pneumonia/ventilator-associated pneumonia.

pneumonia, which could be severe acute respiratory syndrome (SARS) or avian influenza.[61] Endemic fungi (coccidioidomycosis, histoplasmosis, and blastomycosis) occur in well-defined geographic areas and may present acutely with symptoms that overlap with acute bacterial pneumonia.

NP patients often present with less definitive clinical findings, particularly in those who are mechanically ventilated, and the clinical diagnosis is made in patients with a new or progressive radiographic infiltrate, along with some indication that infection is present (fever, purulent sputum, or leukocytosis). Recently, the Clinical Pulmonary Infection Score (CPIS) has been applied to patients with VAP. Six criteria are scored on a scale from 0 to 2 for each, and pneumonia is diagnosed with a total score of at least 6 (out of a maximum of 12).[62] The criteria are (1) fever, (2) purulence of sputum, (3) white blood cell count, (4) oxygenation, (5) degree of radiographic abnormality, and (6) the presence of pathogens in the sputum. Many studies have documented that VAP is diagnosed more often clinically than can be confirmed microbiologically, and the diagnosis is further obscured by the fact that most mechanically ventilated patients are colonized by *enteric gram-negative bacteria*. Thus the finding of potential pathogens in the sputum has no diagnostic value. In addition, some patients can have purulent sputum and fever, without a new infiltrate, and be diagnosed with purulent tracheobronchitis, an infectious complication of mechanical ventilation that may also require antibiotic therapy but is not pneumonia.[2]

In taking a history from a patient with NP, it is important to identify any risk factors for drug-resistant organisms. For ventilated patients, these include prolonged ICU stay (>5 days), recent antibiotic therapy, and the presence of health care–associated pneumonia.[2,44] In CAP patients, risk factors for drug-resistant pneumococcus include recent β-lactam therapy, exposure to a child in daycare, alcoholism, immune suppression, and multiple medical comorbidities.[1,63]

Physical Examination

Physical findings of pneumonia include tachypnea, crackles, rhonchi, and signs of consolidation (egophony, bronchial breath sounds, dullness to percussion). Patients should also be evaluated for signs of pleural effusion. In addition, extrapulmonary findings should be sought to rule out metastatic infection (arthritis, endocarditis, meningitis) or to add to the suspicion of an "atypical" pathogen such as *M. pneumoniae* or *C. pneumoniae,* which can lead to such complications as bullous myringitis, skin rash, pericarditis, hepatitis, hemolytic anemia, or meningoencephalitis. One of the most important ways to recognize severe CAP early in the course of illness is to carefully count the respiratory rate.[64,65] In the elderly, an elevation of respiratory rate can be the initial presenting sign of pneumonia, preceding other clinical findings by as much as 1 to 2 days. Tachypnea is present in more than 60% of all patients, more often in the elderly than in younger patients with pneumonia.[65] In addition, the counting of respiratory rate can identify the patient with severe illness, who commonly has a rate greater than 30 breaths per minute.

ETIOLOGIC PATHOGENS

Community-Acquired Pneumonia

Even with extensive diagnostic testing, an etiologic agent is defined in only about half of all patients with CAP, pointing out the limited value of diagnostic testing and the possibility that we do not know all the organisms that can cause CAP. The most common cause of CAP is pneumococcus *(S. pneumoniae),* an organism which is frequently (at least 40% of the time) resistant to penicillin or other antibiotics, leading to the term *drug-resistant S. pneumoniae* (DRSP). Fortunately, most penicillin resistance in the United States is still more commonly of the "intermediate" type (penicillin minimum inhibitory concentration, or MIC, of 0.1 to 1.0 mg/L) and not of the high-level type (penicillin MIC of 2.0 or more).[66] Pneumococcal resistance to other antibiotics is also common, including macrolides and trimethoprim-sulfamethoxazole, but the clinical relevance and impact on outcome of these in vitro findings is uncertain, and most experts believe that only organisms with a penicillin MIC of greater than 4 mg/L lead to an increased risk of death.[67]

All patients with severe CAP should be considered to be at risk for DRSP and, in addition, those admitted to the ICU can have infection with atypical pathogens, which accounts for up to 20% of infections, either as primary infection or as co-pathogens. The identity of these organisms varies over time and geography. In some areas, *Legionella* is a common cause of severe CAP, whereas in others *Chlamydophila pneumoniae* or *M. pneumoniae* predominate.[68] Other important causes of severe CAP include *H. influenzae; S. aureus*, which includes MRSA (especially after influenza); and enteric gram-negatives (including *P. aeruginosa*) in patients with appropriate risk factors (particularly bronchiectasis and steroid-treated COPD). Recently, a toxin-producing strain of MRSA has been described to cause CAP in patients after influenza and other viral infections. This community-acquired MRSA is biologically and genetically distinct from the MRSA that causes NP, being more virulent and necrotizing and associated with the production of the Panton-Valentine Leukocidin (PVL).[69,70] Viruses can be a cause of severe CAP including influenza virus, as well as parainfluenza virus and epidemic viruses such as coronavirus (which caused SARS) and avian influenza.[61] Viral pneumonia (SARS and influenza) can lead to respiratory failure, and occasionally tuberculosis or endemic fungi can result in severe pneumonia.

Unusual etiologies should be considered, especially in patients who have epidemiologic risk factors for specific pathogens, as discussed earlier. In addition, certain "modifying factors" may be present that increase the likelihood of CAP caused by certain pathogens.[1] Thus the risk factors for DRSP include β-lactam therapy in the past 3 months, alcoholism, age older than 65 years, immune suppression, multiple medical comorbidities, and contact

with a child in day care.[1,63] Risk factors for gram-negatives include residence in a nursing home, underlying cardiopulmonary disease, multiple medical comorbidities, probable aspiration, recent hospitalization, and recent antibiotic therapy. Many of these patients who are at risk for gram-negatives would now be reclassified as having health care–associated pneumonia (HCAP).[2,13] Some ICU patients are at risk for pseudomonal infection, whereas others are not, and the risk factors for *P. aeruginosa* infection are structural lung disease (bronchiectasis), corticosteroid therapy (>10 mg prednisone/day), broad-spectrum antibiotic therapy for more than 7 days in the past month, previous hospitalization, and malnutrition.[2] Although aspiration has often been considered a risk factor for anaerobic infection, a study of severe CAP in elderly patients with aspiration risk factors found that this population is likely to have gram-negative infection and, using sensitive microbiologic methods, anaerobes were uncommon.[71]

Nosocomial Pneumonia

All patients with this illness are at risk for infection with a group of bacteria referred to as "core organisms," which include pneumococcus, *H. influenzae*, methicillin-sensitive *S. aureus*, and nonresistant gram-negatives (*E. coli*, *Klebsiella* spp., *Enterobacter* spp., *Proteus* spp., and *Serratia marcescens*). In addition, some patients are also at risk for infection with other organisms, depending on the presence of risk factors such as prolonged hospitalization (>5 days), prior antibiotic therapy, recent hospitalization (within 90 days), recent antibiotic therapy, residence in a nursing home, or need for chronic care outside the hospital.[2,44] Patients with these risk factors can possibly be infected with multidrug-resistant (MDR) gram-positive and gram-negative organisms including MRSA, *P. aeruginosa,* and *Acinetobacter* spp. Recognition of the multiple risk factors associated with these resistant pathogens has made it clear that there are patients with "early-onset" NP (within the first 4 days of hospitalization) who can be infected with MDR organisms. In addition, up to 40% of patients with VAP have polymicrobial infection, involving multiple pathogens.[72]

Most data on NP bacteriology come from patients with VAP, and the etiology in nonventilated patients is presumed to be similar on the basis of the presence of risk factors for drug-resistant pathogens. In patients with VAP, infection with enteric gram-negatives is more common than infection with gram-positives, although the frequency of MRSA infection is increasing in this population, as is infection with *Acinetobacter* spp.[73] HCAP patients have been included in the NP guidelines as being a group at risk for infection with MDR gram-positive and gram-negatives.[2] Although most ICU-admitted patients with this illness are infected with these organisms, one study of nursing home patients requiring mechanical ventilation for severe pneumonia showed that these organisms were not present if the patient with severe pneumonia had not received antibiotics in the preceding 6 months and was also of a good functional status (as defined by activities of daily living).[74]

In approaching the bacteriology of NP, it is important to recognize that each hospital, as well as each ICU within a given hospital, can have its own unique flora and antibiotic susceptibility patterns, and thus therapy needs to be adapted to the organisms in a given institution, which can change over time.[75] In addition, it is especially important to know this information because antibiotic resistance is a common factor contributing to initially inappropriate empiric antibiotic therapy. Choosing the wrong empiric therapy has been a particular problem for organisms such as *P. aeruginosa*, *Acinetobacter* spp., and MRSA.[12] These highly resistant organisms can be present in up to 60% of patients who develop VAP after at least 7 days of ventilation and who have also received prior antibiotic therapy.[2,44]

Need for Respiratory Isolation

Patients with certain suspected pathogens should be placed in respiratory isolation to protect both the staff and other patients from infection with these organisms. This includes primarily airborne pathogens that spread via the aerosol route and includes any patient who is suspected of having tuberculosis, influenza, respiratory syncytial virus, or any other epidemic viral infection. Tuberculosis should be considered in any patient with a history of a preceding indolent pneumonia and in those with severe pneumonia and a history of HIV infection or recent immigration from endemic areas of infection. Patients with MRSA and highly resistant gram-negatives may need gown, glove, and mask precautions to avoid spread of these difficult-to-treat bacteria.

DIAGNOSTIC ISSUES

Diagnostic testing is performed for two purposes: (1) to define the presence of pneumonia and (2) to identify the responsible pathogen. In all forms of pneumonia, a chest radiograph is used to identify the presence of a lung infiltrate, but in some clinical settings, especially in suspected VAP, there can be noninfectious causes for the radiographic abnormality. Chest radiographic patterns are generally not useful for identifying the etiology of CAP, although findings such as pleural effusion (pneumococcus, *H. influenzae*, *M. pneumoniae*, pyogenic streptococci) and cavitation (*P. aeruginosa*, *S. aureus*, anaerobes, MRSA, tuberculosis) can suggest certain groups of organisms. Defining the etiologic pathogens in patients with CAP is often difficult because up to half of all such patients have no identified etiology, even with extensive diagnostic testing including cultures of blood and sputum. On the other hand, those with VAP commonly have bacteria present in samples of lower respiratory tract secretions, but the presence of a positive culture cannot reliably distinguish infection from colonization.

Community-Acquired Pneumonia

For patients with CAP, a chest radiograph not only confirms the presence of pneumonia but can be used to identify complicated and severe illness, if the patient has findings such as multilobar infiltrates, cavitation, or a

loculated pleural effusion (suggesting an empyema). Although diagnostic testing is valuable in patients with CAP, therapy should never be delayed for the sole purpose of facilitating testing because delays in therapy have been associated with increased mortality. All CAP patients admitted to the ICU should have a chest radiograph, blood and lower respiratory tract (sputum, endotracheal aspirate, bronchoalveolar lavage, or bronchoscopic specimen) cultures, an arterial blood gas, and routine hematologic and blood chemistry testing. If the patient has a moderate-sized pleural effusion, this should be tapped and the fluid sent for culture and biochemical analysis. Patients with severe CAP should have two sets of blood cultures, and these are more likely to be positive if the patient has not received antibiotics at the time of sampling or if there are signs of systolic hypotension, tachycardia, dehydration, or an elevated white blood cell count.[76] The presence of bacteremia may not worsen prognosis but does allow identification of drug-resistant organisms, and most positive blood cultures in CAP reveal *Pneumococcus*.

Sputum culture should be accompanied by a Gram stain to guide interpretation of the culture results, but not to focus initial antibiotic therapy. In some situations, Gram stain can be used to broaden initial empiric therapy by enhancing the suspicion for organisms that are not covered in routine empiric therapy (such as *S. aureus* being suggested by the presence of clusters of gram-positive cocci, especially during a time of epidemic influenza). Routine serologic testing is not recommended. However, in patients with severe illness, the diagnosis of *Legionella pneumophila* can be made by urinary antigen testing, which is the test that is most likely to be positive at the time of admission, but a test that is specific only for serogroup I infection.[1,77] Examination of concentrated urine for pneumococcal antigen may also be valuable. Bronchoscopy is not indicated as a routine diagnostic test but may be necessary in some patients with severe forms of CAP to establish an etiologic diagnosis. In these patients the results of diagnostic testing can often be used to focus the initially broad-spectrum empiric therapy to a simpler regimen.[78]

Nosocomial Pneumonia

NP is diagnosed when a patient has been in the hospital for at least 48 to 72 hours and then develops a new or progressive infiltrate on chest radiograph, accompanied by at least 2 of the following 3: fever, leukocytosis, and purulent sputum. As mentioned, these clinical findings may be sensitive but not specific for infection, and efforts to improve the clinical diagnosis of pneumonia have involved the previously mentioned CPIS.[79] Many patients with suspected NP can have other diagnoses that can be suggested by the rapidity of the clinical response and by the nature of the clinical findings. These diagnoses include atelectasis and congestive heart failure (rapid clinical resolution) or, in the case of a lack of response to therapy, inflammatory lung diseases, extrapulmonary infection (sinusitis, central line infection, intraabdominal infection), or the presence of an unusual or drug-resistant pathogen. In addition, the presence of pathogenic organisms in sputum culture is not diagnostic because this finding cannot separate oropharyngeal and tracheobronchial colonization from parenchymal lung infection. The situation is further complicated because some ventilated patients can have nosocomial infectious tracheobronchitis, an illness with all the clinical features of pneumonia but with no new lung infiltrate, and this illness may also require antibiotic therapy and involve the same pathogens as VAP.[2]

In an effort to make the diagnosis more secure, and to avoid the overuse of antibiotics, some investigators have used quantitative sampling of lower respiratory secretions collected either bronchoscopically (bronchoalveolar lavage, protected specimen brush) or nonbronchoscopically (endotracheal aspirate, nonbronchoscopic catheter lavage), particularly in patients with suspected VAP. When quantitative cultures are collected, some investigators have defined the presence of pneumonia by the growth of bacteria at a concentration above a predefined threshold concentration.[4,5] Although the results can guide therapy decisions, most clinicians use antibiotic therapy, regardless of quantitative culture data, in patients who have clinical signs of sepsis and suspected pneumonia. Regardless of whether quantitative cultures are used, all patients with suspected NP should have a lower respiratory tract culture collected prior to the start of antibiotic therapy. If this is not a quantitative culture, then a sputum or tracheal aspirate should be obtained and the findings reported "semiquantitatively" as light, moderate, or heavy growth of bacteria.[2,5] Unfortunately, a negative culture is difficult to interpret if the patient has had initiation or change in antibiotic therapy in the preceding 72 hours. If, however, either a quantitative or semiquantitative culture is negative or does not show a highly resistant pathogen, and antibiotics have not been changed in the past 72 hours, the therapy can often be stopped or focused to a narrower spectrum.[2,80]

THERAPY

For all patients with severe pneumonia, algorithms for initial empiric therapy have been developed on the basis of the most likely etiologic pathogens in a given patient and clinical setting. If diagnostic testing reveals a specific etiologic pathogen, therapy can be focused on the results. In addition, as mentioned earlier, if an anticipated pathogen is not present in a diagnostic sample, it may be possible to stop empiric coverage of that organism (Fig. 43-1).

General Considerations

Until recently, combination empiric antibiotic therapy for severe pneumonia was universally given by physicians working in ICUs. The rationale for this approach was to provide broad antimicrobial coverage, prevent the emergence of resistance during therapy, and potentially provide synergistic activity if a β-lactam antibiotic was combined with an aminoglycoside (for *P. aeruginosa* pneumonia). However, only with bacteremic *P. aeruginosa* pneumonia has combination therapy (generally with an aminoglycoside and a β-lactam) been shown to be

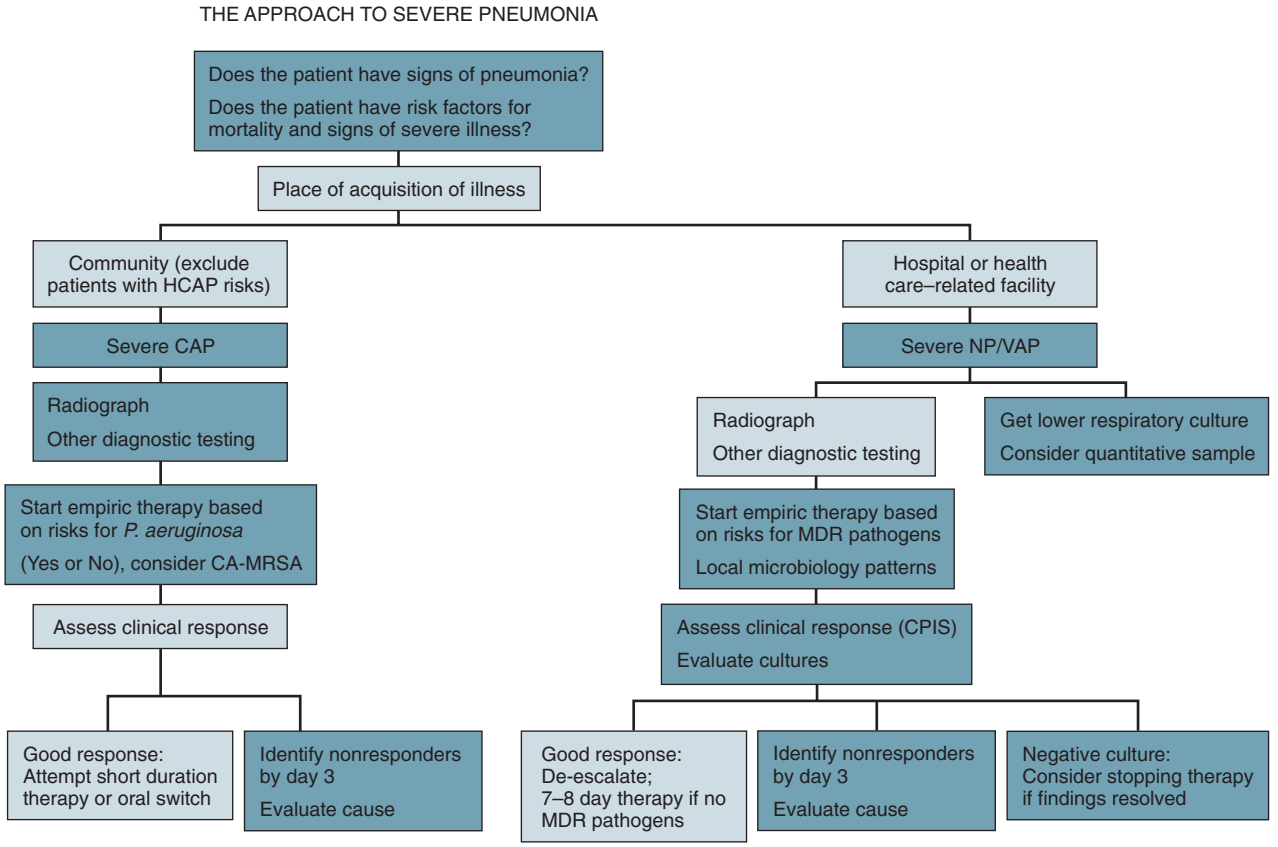

Figure 43-1. Algorithmic approach to managing severe pneumonia. Patients are categorized into community-acquired pneumonia and nosocomial pneumonia/ventilator-associated pneumonia. Each group undergoes diagnostic testing, followed by empiric therapy based on the most likely etiologic pathogens. The resulting clinical response is used to guide the duration of therapy or to decide whether to broaden the differential diagnosis to other processes. CA-MRSA = community-acquired MRSA; CAP = community-acquired pneumonia; MDR = multidrug resistant; NP = nosocomial pneumonia; VAP = ventilator-associated pneumonia.

superior to monotherapy.[81,82] One practical problem to this approach is the aminoglycosides themselves, a class of antibiotics with a narrow therapeutic-to-toxic ratio, and a high incidence of nephrotoxicity, particularly in elderly patients. When these drugs are used, it is important to use enough antibiotic to achieve high peak serum levels to optimize efficacy but to also avoid elevated trough levels, which correlate with toxicity. When peak serum levels have been monitored, levels of more than 7 μg/mL for gentamicin and tobramycin and more than 28 μg/mL for amikacin have been associated with more favorable outcomes.[83]

One other limitation of aminoglycosides is their relatively poor penetration into bronchial secretions, achieving only 40% of the serum concentrations at this site. In addition, antimicrobial activity is reduced at the low pH levels that are common in the bronchial secretions of patients with pneumonia. These concerns may explain the finding in one study that the addition of an aminoglycoside to imipenem had no added efficacy for severe NP and only added renal toxicity.[84] In addition, a meta-analysis of the value of adding an aminoglycoside to a β-lactam in critically ill patients, including many with pneumonia, found no therapeutic benefit.[82] It has now become standard to administer aminoglycosides by combining the total 24-hour dose into a single dose, rather than in divided doses.

This approach is theoretically possible because of the prolonged postantibiotic effect of aminoglycosides, and it is hoped that once-daily dosing can improve efficacy, reduce (or at least not increase) toxicity, and reduce the need for monitoring of serum levels. In one meta-analysis, this approach proved to have little advantage with regard to efficacy or safety.[85] Despite these findings, if aminoglycosides are used, once-daily dosing is recommended because it is simpler and requires less intensive monitoring (measuring only trough levels).

Recently, the development of newer cephalosporins, carbapenems, other β-lactams, and quinolones with high potency and broad antibacterial activity, as well as resistance to degradation by bacterial β-lactamases, has permitted the introduction of monotherapy, even in the patient with severe NP, provided that certain high-risk organisms are absent (*P. aeruginosa*, *Acinetobacter* spp., and MRSA). In the absence of these highly resistant pathogens, antibiotics that have been effective as monotherapy for severe VAP include imipenem, meropenem, cefepime, ciprofloxacin, high-dose levofloxacin (750 mg daily), and piperacillin/tazobactam.[2,86-90] In the patient with severe pneumonia, it is usually necessary to start

therapy with multiple agents, but after tracheal aspirate or other lower respiratory tract cultures become available, it is usually possible to "de-escalate" to monotherapy, particularly if a highly resistant organism is absent.[80]

In some circumstances monotherapy should not be used: (1) in any patient with severe CAP because the efficacy of this approach has not been demonstrated; (2) in suspected bacteremic infection with *P. aeruginosa;* (3) in the empiric therapy of VAP, if the patient has risk factors for infection with MDR pathogens; and (4) if the patient has NP and both *S. aureus* and *P. aeruginosa* are identified in culture as the etiologic pathogens. Monotherapy should never be attempted with a third-generation cephalosporin because of the possibility of emergence of resistance during therapy as a result of production of chromosomal β-lactamases by the *Enterobacteriaceae* group of organisms.[2]

If *P. aeruginosa* is a target organism of therapy, antibiotics with efficacy against this pathogen are necessary. Anti-pseudomonal β-lactam antibiotics include the penicillins piperacillin, azlocillin, mezlocillin, ticarcillin, and carbenicillin; the third-generation cephalosporins ceftazidime and cefoperazone; the fourth-generation cephalosporin cefepime; the carbapenems imipenem and meropenem; the monobactam aztreonam (which can be used in the penicillin-allergic patient); and the β-lactam/β-lactamase inhibitor combinations ticarcillin/clavulanate and piperacillin/tazobactam. Other antipseudomonal agents include the quinolone ciprofloxacin; high-dose levofloxacin; and the aminoglycosides (amikacin, gentamicin, tobramycin).

Community-Acquired Pneumonia

For ICU-admitted CAP, initial therapy should be directed at DRSP, *Legionella* and other atypical pathogens, enteric gram-negatives, and other selected organisms on the basis of epidemiologic risk assessment. Therapy is chosen, depending on whether or not the patient is at risk for *P. aeruginosa* ("modifying" risk factors listed earlier). In all the treatment algorithms, no ICU-admitted CAP patient should receive empiric monotherapy, even with one of the new quinolones.[1] This recommendation is based on the fact that the efficacy (especially for meningitis complicating pneumonia), effective dosing and safety of quinolone monotherapy has not been established for ICU-admitted CAP patients. In one recent study comparing levofloxacin with a β-lactam/quinolone combination, the single-agent regimen was not shown to be effective for patients in septic shock and for those treated with mechanical ventilation.[91]

Recommended therapy for severe CAP, in the absence of pseudomonal risk factors, should be with a selected intravenous β-lactam (e.g., cefotaxime, ceftriaxone, ertapenem, a β-lactam/β-lactamase inhibitor combination) combined with either an intravenous macrolide or an intravenous antipneumococcal quinolone (levofloxacin or moxifloxacin). For patients with pseudomonal risk factors, therapy can be with a two-drug regimen using an anti-pseudomonal β-lactam (imipenem, meropenem, piperacillin/tazobactam, cefepime) plus ciprofloxacin (the most active anti-pseudomonal quinolone) or levofloxacin (750 mg daily). An alternative is a three-drug regimen using an anti-pseudomonal β-lactam plus an aminoglycoside plus either an intravenous antipneumococcal quinolone (levofloxacin or moxifloxacin) or a macrolide.[1,92]

In addition to the antibiotic approach to therapy outlined earlier, there are several other considerations in the management of CAP. These include providing the first dose of therapy as soon as possible (within 4 hours of arrival in the hospital) and providing coverage in all patients for atypical pathogens using either a macrolide or a quinolone in the regimen on the basis of the data that such an approach reduces mortality.[26,27,93] Even in patients with pneumococcal bacteremia, the use of combination therapy (generally with the addition of atypical pathogen coverage to pneumococcal coverage) has been associated with reduced mortality compared with monotherapy.[93] In addition, certain adjunctive therapies should be considered including oxygen, chest physiotherapy (if at least 30 mL of sputum daily and a poor cough response), aerosolized bronchodilators, and corticosteroids (if hypotension and possible relative adrenal insufficiency are present). An analysis of the use of activated protein C for patients with septic shock demonstrated that 35% of the patients in the pivotal clinical trial had underlying CAP and that activated protein C was most effective for those CAP patients with an APACHE II score of greater than 25, a PSI class of IV or V, and a CURB-65 score of at least 2. Patients with pneumococcal infection and inadequate therapy also benefited, although the benefit was minimal in those treated with adequate therapy.[94] In addition to their value in patients with relative adrenal insufficiency, corticosteroids may be helpful in severe CAP because of their immunomodulating effect. One randomized controlled trial of 48 patients compared hydrocortisone infusion (240 mg/day) with placebo and found that steroid therapy reduced mortality, length of stay, and duration of mechanical ventilation.[95] These findings require other studies to confirm the benefit of this adjunctive therapy.

Information on the proper duration of therapy in patients with CAP, especially those with severe illness, is scarce. Even in the presence of pneumococcal bacteremia, short durations of therapy may be possible, with a rapid switch from intravenous to oral therapy in responding patients. Generally, *S. pneumoniae* can be treated for 5 to 7 days if the patient is responding rapidly and has received accurate empiric therapy at the correct dose. The presence of extrapulmonary infection (such as meningitis) and the identification of certain pathogens (e.g., bacteremic *S. aureus*, *P. aeruginosa*) may require longer durations of therapy. Identification of *L. pneumophila* pneumonia may require at least 14 days of therapy, depending on severity of illness and host defense impairments, although recent data have shown that quinolone therapy may be the best approach to management and that durations as short as 5 days with levofloxacin 750 mg may be effective.[96] The switch to oral therapy, even in severely ill patients, may be facilitated by the use of quinolones, which are highly bioavailable and achieve the

same serum levels with oral therapy as with intravenous therapy.

Currently, there is controversy about the need for empiric therapy directed against community-acquired MRSA. Most experts recommend that this organism be targeted in patients with severe, necrotizing CAP following a viral illness, particularly influenza. Optimal therapy has not been defined. Vancomycin alone may not be sufficient and has led to clinical failure, presumably because it is not active against the PVL toxin that accompanies community-acquired MRSA. For this reason, it may be necessary to add clindamycin to vancomycin or to use linezolid because both of these latter agents can inhibit toxin production.[70]

Nosocomial Pneumonia

Antibiotic therapy should be given promptly at the first clinical suspicion of pneumonia, and empiric therapy should be dictated by considering whether the patient is at risk for infection with MDR pathogens, primarily because of the presence of recent antibiotic therapy, a prolonged hospital stay, or the development of infection after residing in a nursing home or other chronic care setting (such as a dialysis center) or if there are other risk factors for HCAP. Patients without risks for MDR pathogens can be treated for the "core pathogens" listed earlier, generally with a monotherapy regimen of a second-generation or non-pseudomonal third-generation cephalosporin, a β-lactam/β-lactamase inhibitor combination, ertapenem, or a quinolone (levofloxacin or moxifloxacin).[2] If the patient is allergic to penicillin, therapy can be with a quinolone or the combination of clindamycin and aztreonam. Probably not all HCAP patients need therapy directed against MDR pathogens, and monotherapy has been successful in the absence of MDR pathogens. MDR pathogens are not likely in HCAP patients who do not have at least two of the following: severe infection, recent antibiotic therapy in the past 6 months, poor functional status.[71]

In the selection of an empiric therapy regimen, it is necessary to know which antibiotic the patient has recently received (within the past 14 days) and to choose an agent that is in a different class because repeated use of the same class of antibiotic may drive resistance to that class, especially if the pathogen is *P. aeruginosa*.[97] Similar findings have been made for patients with bacteremic pneumococcal pneumonia and CAP, and repeat use of an agent within 3 months may mean that the patient is being treated with an agent to which pneumococcus is more likely to be resistant.[98] In addition, the recent use of quinolones may present a particular problem because, in the ICU, recent quinolone therapy may predispose to not only quinolone-resistant organisms but also to infection with MDR pathogens, extended-spectrum β-lactamase producing gram-negatives, and MRSA.[99] For all patients with VAP, it is important to use the correct dose of antibiotic (see Box 43-4 for recommended doses for patients with normal renal function).[2]

Although it is possible to identify, on the basis of risk factors, the patient who is likely to be infected with MDR pathogens, it is important to realize that each hospital and each ICU has its own unique organisms and patterns of antimicrobial resistance and that these patterns change over time. Therefore it is necessary to monitor local patterns of resistance and to choose empiric therapy that is likely to be effective in a given clinical setting.[75] One other concept that has been incorporated into some studies of empiric therapy is that of "antibiotic rotation," which means the standard empiric regimens are intentionally varied over time to expose bacteria to different antibiotics and thus minimize the selection pressure for resistance. In some studies this approach has been effective in reducing the incidence of infection with resistant organisms.[100] One limitation of antibiotic rotation is that it may mean the use of the same regimen repeatedly in the same patient, and this may itself be a risk factor for selecting for resistance. In addition, there are unanswered questions about how long each cycle of therapy should last, what agents should be cycled, how effective the approach is for medical versus surgical patients, and whether cycling should focus on gram-positive and gram-negative organisms.[101]

Patients at risk for MDR pathogens generally require combination therapy rather than monotherapy. Combination therapy is most valuable because it provides broad-spectrum coverage, thereby minimizing the chance of initially inappropriate therapy. Recent data have shown that combination therapy using an aminoglycoside with a β-lactam is no more effective than monotherapy with a β-lactam for severe infections including those caused by *P. aeruginosa*, but dual-pseudomonal therapy is still recommended for patients at risk for this pathogen in order to minimize the chance of initially ineffective therapy.[2,82] The empiric therapy for patients at risk for MDR pathogens should include an aminoglycoside or quinolone (ciprofloxacin or high-dose levofloxacin) plus an anti-pseudomonal β-lactam (imipenem, meropenem, piperacillin/tazobactam, aztreonam, or cefepime). If the patient is at risk for a second ICU-acquired infection (and most are), it may be prudent to use an aminoglycoside for the first episode of infection, reserving the quinolone for

Box 43-4

Doses of Selected Antibiotics for Ventilator-Associated Pneumonia (Normal Renal Function)

Ciprofloxacin: 400 mg every 8 hours; Levofloxacin 750 mg every day
Imipenem 1 gm every 8 hours or 500 mg every 6 hours; meropenem 1 gm every 6 to 8 hours
Piperacillin/tazobactam 4.5 gm every 6 hours
Cefepime 1 to 2 gm every 8 to 12 hours
Ceftazidime 2 gm every 8 hours
Gentamicin or tobramycin 7 mg/kg/d or amikacin 20 mg/kg/d
Linezolid 600 mg every 12 hours
Vancomycin 15 mg/kg every 12 hours

any subsequent infection, because of concern about quinolone induction of MDR, which could limit subsequent therapy options.[102] If the patient is suspected of having MRSA because of a tracheal aspirate Gram stain showing gram-positive organisms or because of other risk factors, a third drug should be added. This could be either linezolid or vancomycin, and recent data have suggested the superiority of linezolid for both survival and clinical cure in patients who have been documented to have MRSA VAP.[103]

Many patients with NP will get an initial empiric therapy that is broad-spectrum, and thus it is important to consider "de-escalation" of the initial regimen as serial clinical and microbiologic data become available (see Fig. 43-1).[80] If the patient has received a broad-spectrum regimen and the cultures do not show MDR organisms, then the patient can finish therapy with any of six monotherapy regimens that have been documented to be effective for severe VAP, in the absence of MDR organisms: ciprofloxacin, imipenem, meropenem, piperacillin/tazobactam, cefepime, and high-dose levofloxacin. If *P. aeruginosa* is present, combination therapy with a β-lactam and aminoglycoside should continue for 5 days, after which the patient can be switched to monotherapy with an agent to which the organism is sensitive.[2] When de-escalation has been used, meaning either the switch to a more narrow spectrum regimen, the use of fewer drugs, or both, mortality in VAP has been reduced, compared with when patients do not have de-escalation.[37,38,80] Many unrealized opportunities exist for using this approach in patients with *P. aeruginosa* infection and sensitive pathogens and in those with a good clinical response and negative respiratory tract cultures.[80]

If the lower respiratory tract cultures are negative, it may be possible to stop therapy (especially if an alternative diagnosis is suspected) or to shorten the duration of therapy. In addition, if cultures show that the initial empiric regimen was appropriate and if the patient has a good clinical response (reflected by a drop in the CPIS), then it may be possible to reduce the duration of therapy to as little as 7 to 8 days, although this may not be pos-sible if the etiologic pathogen is *P. aeruginosa* or MRSA.[104]

Adjunctive therapeutic measures are necessary in some patients including chest physiotherapy, aerosolized bronchodilators, and mucolytic agents. For selected patients who are infected with highly resistant organisms and are not responding to systemic antibiotics, it may be valuable to add aerosolized antibiotics (e.g., gentamicin, tobramycin, colistin, ceftazidime). Aerosolized administration of antibiotics offers the advantage of achieving high concentrations of antibiotics at the site of infection. As a result, it may be possible to overcome the problems of poor lung penetration of certain agents (aminoglycosides) and provide the high levels of antibiotics that are necessary to kill certain resistant organisms. Locally administered antibiotics are rarely absorbed, and systemic toxicity is minimized. Despite these theoretical advantages, many efficacy questions remain to be answered by clinical trials. Pending more information, locally instilled or aerosolized antibiotics are not usually recommended for routine treatment of pneumonia but may have a role as adjunctive therapy in patients with MDR organisms not responding to systemic therapy.[105]

EVALUATION OF NONRESPONDING PATIENTS

Because pneumonia is a clinical syndrome, not all patients with this diagnosis actually have lung infection and some may be infected with an unusual or nonsuspected pathogen. In addition, some patients can develop complications of the illness or its therapy, and all of these situations may lead to an apparent nonresponse to therapy.

With effective therapy, most patients with CAP become afebrile by days 3 to 5, and most have a clinical response by day 3. Similarly, even with VAP, most patients have some improvement, particularly in oxygenation, by day 3.[2,62] Nonresponding patients with either CAP or VAP should be evaluated for alternative diagnoses (inflammatory lung disease, atelectasis, heart failure, malignancy, pulmonary hemorrhage, pulmonary embolus, a nonpneumonic infection); a resistant or unusual pathogen (including tuberculosis and fungal infection); a pneumonia complication (empyema, lung abscess, drug fever, antibiotic-induced colitis); or a secondary site of infection (central line infection, intra-abdominal infection) (Box 43-5). The evaluation of a nonresponding patient should be individualized but may include CT scanning of the

Box 43-5

Mimics of Infectious Pneumonia in the Mechanically Ventilated Patient: Consider in the Nonresponding Patient

Nonpneumonia Diagnoses

Primary pulmonary malignancy: lung cancer, lymphoma
Metastatic cancer: including tumor emboli, lymphangitic spread of cancer
Pulmonary vasculitis: including Wegener's granulomatosis, Goodpasture's syndrome
Alveolar hemorrhage
Pulmonary emboli and/or infarction
Atelectasis
Pleural effusion
Acute respiratory distress syndrome
Heart failure
Extrapulmonary infection: central line, intra-abdominal
Lung contusion after thoracic trauma

Iatrogenic Processes

Drug-induced pneumonitis
Aspiration of enteral feeding
Pulmonary artery catheter complications
Hemorrhage
Infarction
Pneumothorax

chest, pulmonary angiography, bronchoscopy, and occasionally open lung biopsy.

PREVENTION

Prevention of CAP is important for all groups of patients, especially the elderly patient, who is at risk for both a higher frequency of infection and a more severe course of illness. Appropriate patients should be vaccinated with both pneumococcal and influenza vaccines, and cigarette smoking should be stopped in all at-risk patients. Even for the patient who is recovering from CAP, immunization while in the hospital is appropriate to prevent future episodes of infection. The evaluation of all patients for vaccination need and the provision of information about smoking cessation are now performance standards used to evaluate the hospital care of CAP patients. If there is uncertainty about whether the patient has recently been vaccinated, it is probably best to give a pneumococcal vaccination because repeat administration, even more often than recommended, is not generally associated with an adverse reaction.[106] Hospital-based immunization is recommended. One study found that among 1633 patients with pneumonia treated in the hospital, 62% had been hospitalized in the preceding 4 years.[107] In addition, 80% of these patients had a high-risk condition that would have qualified them to receive pneumococcal vaccine. On the basis of these observations, it seems likely that many cases of CAP could be prevented if pneumococcal vaccine were given to all hospitalized patients who qualify for the vaccine, regardless of why they are hospitalized.

Although no single method can reliably prevent NP, multiple small interventions may have benefit, especially those focused on modifiable risk factors for infection. Recently, these interventions have been combined into "ventilator bundles," which have been demonstrated to reduce the incidence of VAP if applied carefully.[108,109] Most of these bundles include multiple interventions, so it is difficult to know which individual manipulations are most valuable. Successful bundles have included interventions such as elevation of the head of the bed to 30 degrees (to avoid the risk of aspiration present with the supine position), daily interruption of sedation to attempt weaning, peptic ulcer disease prophylaxis, endotracheal tube suctioning (possibly with a closed suction system), hand washing, careful oral care, and tight control of blood glucose.[110] Despite the success of this approach, one recent randomized study has demonstrated a lack of benefit and feasibility of routine head-of-the-bed elevation.[111]

Other widely used measures in mechanically ventilated patients are avoidance of large inocula of bacteria into the lung (careful handling of ventilator circuit tubing); mobilization of respiratory secretions (frequent suctioning, use of rotational bed therapy in selected individuals); nutritional support (enteral preferred over parenteral); placing of feeding tubes into the small bowel (to avoid aspiration, which is more likely with stomach tubes); and avoidance of large gastric residuals when giving enteral feeding. In addition, any tube inserted into the stomach or trachea should be inserted through the mouth and not the nose, whenever possible, to avoid obstructing the nasal sinuses and prevent nosocomial sinusitis, which can lead to NP.[110] A specially adapted endotracheal tube that allows for continuous aspiration of subglottic secretions may interrupt the oropharyngeal to tracheal transfer of bacteria and reduce the incidence of pneumonia.[112] Because endotracheal intubation is a risk for pneumonia, noninvasive positive pressure ventilation should be used whenever possible. This approach is associated with a lower pneumonia risk than traditional mechanical ventilation. Prophylactic systemic or topical antibiotics have no specific role, but some data suggest that patients with coma caused by stroke or head trauma and those who may have aspirated during an emergent intubation may benefit from a 24-hour course of systemic antibiotics.[113] "Selective digestive decontamination," which includes systemic and topical intestinal antibiotics, remains controversial as a method to reduce the incidence of pneumonia. Literature support exists in some selected populations. This approach carries the risk of promoting antibiotic resistance.[2]

KEY POINTS

- NP is the hospital-acquired infection most likely to lead to the death of patients. Typically the crude mortality rate of this infection is 50%, with even higher rates seen in patients who are mechanically ventilated. Of all patients who die with NP, from one third to one half of these deaths are the direct result of infection termed "attributable mortality."
- A good, simple predictor of a poor outcome from CAP is the presence of at least 3 of the CURB-65 indicators: confusion, admission blood urea nitrogen greater than 19.6 mg/dL, low blood pressure (systolic blood pressure <90 mm Hg, or diastolic blood pressure lower than 60 mm Hg), a respiratory rate higher than 30 breaths per minute, and age of at least 65.
- The most important risk factor for mortality in patients with VAP is inappropriate antibiotic therapy. Other risk factors for mortality include respiratory failure, coma on admission, bilateral radiographic abnormalities, and infection with resistant organisms.
- A number of common therapeutic interventions increase the risk of hospital-acquired pneumonia and should be chosen carefully. These include endotracheal intubation, corticosteroids, antibiotics, immunosuppressives, total parenteral nutrition, and certain strategies for feeding enterally and providing prophylaxis for intestinal bleeding.
- The most common pathogen for CAP is pneumococcus, with *Legionella pneumophila* and other atypical pathogens being a major concern in patients with severe CAP.
- Enteric gram-negative bacteria are the most common pathogens causing NP, but MDR pathogens including gram-negatives and *Staphylococcus aureus* (including MRSA) can also occur, particularly when the patient has been in the hospital for at least 5 days and has received antibiotic therapy before the onset of pneumonia.

- NP is often treated after making a clinical diagnosis, but this clinical approach is overly sensitive, and some patients who satisfy a clinical definition of pneumonia will have other disease processes.
- Invasive diagnostic methods can be used to quantify the bacteriology of NP patients but may not always identify all patients with pneumonia, particularly in the presence of prior antibiotic therapy. Methodologic questions make these tools controversial in patient management, and it is uncertain if they favorably alter patient outcome.
- Each ICU has its own unique bacteriology, and this information should be considered when choosing empiric therapy of NP.
- In choosing an antibiotic for a patient with severe pneumonia, take a history of recent antibiotic use and avoid using any agent prescribed in the past 3 months for a patient with CAP and any agent prescribed in the past 2 weeks for a patient with VAP.
- Although initial empiric antibiotic therapy of severe pneumonia is necessarily broad-spectrum, efforts should be made to re-evaluate clinical response and microbiologic data to narrow the spectrum of therapy and the number of drugs. This can usually be done after 3 days, and patients with a good clinical response can have the duration of therapy reduced to 7 to 10 days.
- If the patient has not improved after 3 days of therapy, it is necessary to determine if there is another disease process other than pneumonia or if the infection is caused by a drug-resistant or unsuspected pathogen.
- In treating patients with severe pneumonia it is important to use the correct dose of the correct antibiotic. Using too low a dose can be a factor leading to poor outcome.
- CAP can be prevented by the use of vaccines, particularly in hospital-based programs. The most widely used strategy for NP prevention is the use of "ventilator bundles," which may be valuable if carefully applied, but the impact of each individual component is unknown.

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