Chapter 121: Pneumonia

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DEFINITION

Pneumonia is an infection of the pulmonary parenchyma. Despite being the cause of significant morbidity and mortality, it is often misdiagnosed, mistreated, and underestimated. Pneumonia historically was typically classified as community-acquired (CAP), hospital-acquired (HAP), or ventilator-associated (VAP). A fourth category, health care–associated pneumonia (HCAP), was introduced recently. This category was meant to encompass those cases of CAP that were caused by multidrug-resistant (MDR) pathogens typically associated with HAP. Unfortunately, the original definitions appear to have been overly sensitive, resulting in the treatment of a high proportion of patients who had community-onset pneumonia with broad-spectrum antibiotics consistent with HAP treatment. Retrospective studies have actually suggested a worse outcome when broad-spectrum antibiotics were used in these cases.

Rather than relying on a predefined subset or category of pneumonia cases, it is likely to be of greater value to assess each case individually on the basis of risk factors for infection with an MDR organism. Rather than originating in primary pneumonia research, the original HCAP definition was modified from a study of health care–associated bacteremia. Recent studies have more closely identified patients at risk for pathogens resistant to the antibiotics usually used; have defined risk factors for infection with methicillin-resistant *Staphylococcus aureus* (MRSA) independent of other MDR pathogens; and have found that at least two, if not three, risk factors are required before the probability of drug-resistant pathogens is sufficient to influence initial empirical broad-spectrum antibiotic therapy. These risk factors are listed in **Table 121-1**.

TABLE 121-1

Risk Factors for Pathogens Resistant to Usual Therapy for Community-Acquired Pneumonia[a]

MULTIDRUG-RESISTANT GRAM-NEGATIVE BACTERIA AND MRSA	NOSOCOMIAL MRSA	COMMUNITY-ACQUIRED MRSA
Hospitalization ≥2 days in previous 90 days	Hospitalization ≥ 2 days in previous 90 days	Cavitary infiltrate or necrosis
Use of antibiotics in previous 90 days	Use of antibiotics in previous 90 days	Gross hemoptysis
Immunosuppression	Chronic hemodialysis in previous 30 days	Neutropenia
Nonambulatory status	Documented prior MRSA colonization	Erythematous rash
Tube feedings	Congestive heart failure	Concurrent influenza
Gastric acid suppression	Gastric acid suppression	Young, previously healthy status
Severe COPD or bronchiectasis[b]		Summer-month onset

[a]Cephalosporin/macrolide or respiratory fluoroquinolone. [b]Risk for Pseudomonas aeruginosa infection.

Abbreviations: COPD, chronic obstructive pulmonary disease; MRSA, methicillin-resistant *Staphylococcus aureus*.

This chapter deals with pneumonia in patients who are not considered to be immunocompromised. **Pneumonia in severely immunocompromised patients, some of whom overlap with the groups of patients considered in this chapter, warrants separate discussion (see Chaps. 70, 138, and 197).**

PATHOPHYSIOLOGY

Pneumonia results from the proliferation of microbial pathogens at the alveolar level and the host's response to those pathogens. Microorganisms gain access to the lower respiratory tract in several ways. The most common is by aspiration from the oropharynx. Small-volume aspiration occurs frequently during sleep (especially in the elderly) and in patients with decreased levels of consciousness. Rarely, pneumonia occurs via hematogenous spread (e.g., from tricuspid endocarditis) or by contiguous extension from an infected pleural or mediastinal space.

Mechanical factors are critically important in host defense. The hairs and turbinates of the nares capture larger inhaled particles before they reach the lower respiratory tract. The branching architecture of the tracheobronchial tree traps microbes on the airway lining, where mucociliary clearance and local antibacterial factors either clear or kill the potential pathogen. The gag and cough reflexes offer critical protection from aspiration. In addition, the normal flora adhering to mucosal cells of the oropharynx, whose components are remarkably constant, prevents pathogenic bacteria from binding and thereby decreases the risk of pneumonia.

When these barriers are overcome or when microorganisms are small enough to be inhaled to the alveolar level, resident alveolar macrophages are extremely efficient at clearing and killing pathogens. Macrophages are assisted by proteins that are produced by the alveolar epithelial cells (e.g., surfactant proteins A and D) and that have intrinsic opsonizing properties or antibacterial or antiviral activity. Once engulfed by the macrophage, the pathogens—even if they are not killed—are eliminated via either the mucociliary elevator or the lymphatics and no longer represent an infectious challenge. Only when the capacity of the alveolar macrophages to ingest or kill the microorganisms is exceeded does clinical pneumonia become manifest. In that situation, the alveolar macrophages initiate the inflammatory response to bolster lower respiratory tract defenses. The host inflammatory response, rather than proliferation of microorganisms, triggers the clinical syndrome of pneumonia. The release of inflammatory mediators, such as interleukin 1 and tumor necrosis factor, results in fever. Chemokines, such as interleukin 8 and granulocyte colony-stimulating factor, stimulate the release of neutrophils and their attraction to the lung, producing both peripheral leukocytosis and increased purulent secretions. Inflammatory mediators released by macrophages and the newly recruited neutrophils create an alveolar capillary leak equivalent to that seen in acute respiratory distress syndrome, although in pneumonia this leak is localized (at least initially). Even erythrocytes can cross the alveolar–capillary membrane, with consequent hemoptysis. The capillary leak results in a radiographic infiltrate and rales detectable on auscultation, and hypoxemia results from alveolar filling. Moreover, some bacterial pathogens appear to interfere with the hypoxemic vasoconstriction that would normally occur with fluid-filled alveoli, and this interference can result in severe hypoxemia. Increased respiratory drive in the systemic inflammatory response syndrome (**Chap. 297**) leads to respiratory alkalosis. Decreased compliance due to capillary leak, hypoxemia, increased respiratory drive, increased secretions, and occasionally infection-related bronchospasm all lead to dyspnea. If severe enough, the changes in lung mechanics secondary to reductions in lung volume and compliance and the intrapulmonary shunting of blood may cause respiratory failure and death.

The presence of a normal alveolar microbiota raises the possibility of an alternative pathway for development of pneumonia. This microbiota is similar to the oropharyngeal microbiota; both are predominantly gram-positive in contrast to the gram-negative milieu of the normal gastrointestinal microbiota. Rather than invasion of a sterile lower respiratory tract by pathogens to cause pneumonia, alterations in host defense may allow overgrowth of one or more components of the normal bacterial flora. The fact that many CAP pathogens are components of the normal alveolar microbiota supports this alternative-pathogenesis model. The two most likely sources of an altered alveolar microbiota are viral upper respiratory tract infections for CAP and antibiotic therapy for HAP/VAP.

PATHOLOGY

Classic pneumonia evolves through a series of pathologic changes. The initial phase is one of *edema*, with the presence of a proteinaceous exudate—and often of bacteria—in the alveoli. This phase is rarely evident in clinical or autopsy specimens because of the rapid transition to the *red hepatization* phase. The presence of erythrocytes in the cellular intra-alveolar exudate gives this second stage its name, but neutrophil influx is more important with regard to host defense. Bacteria are occasionally seen in pathologic specimens collected during this phase. In the third phase, *gray hepatization*, no new erythrocytes are extravasating, and those already present have been lysed and degraded. The neutrophil is the predominant cell, fibrin deposition is abundant, and bacteria have disappeared. This phase corresponds with successful containment of the infection and improvement in gas exchange. In the final phase, *resolution*, the macrophage reappears as the dominant cell type in the alveolar space, and the debris of neutrophils, bacteria, and fibrin has been cleared, as has the inflammatory response.

This pattern has been described best for lobar pneumococcal pneumonia and may not apply to pneumonia of all etiologies, especially viral or *Pneumocystis* pneumonia. In VAP, respiratory bronchiolitis may precede the development of a radiologically apparent infiltrate. Because of the microaspiration mechanism, a bronchopneumonia pattern is most common in nosocomial pneumonias, whereas a lobar pattern is more common in bacterial CAP. Despite the radiographic appearance, viral and *Pneumocystis* pneumonias represent alveolar rather than interstitial processes.

COMMUNITY-ACQUIRED PNEUMONIA

ETIOLOGY

The extensive list of potential etiologic agents in CAP includes bacteria, fungi, viruses, and protozoa. Newly identified pathogens include metapneumoviruses, the coronaviruses responsible for severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), and community-acquired strains of MRSA. Most cases of CAP, however, are caused by relatively few pathogens **(Table 121-2)**. Although *Streptococcus pneumoniae* is most common, other organisms must also be considered in light of the patient's risk factors and severity of illness. Separation of potential agents into "typical" bacterial pathogens or "atypical" organisms may be helpful. The former category includes *S. pneumoniae*, *Haemophilus influenzae*, and (in selected patients) *S. aureus* and gram-negative bacilli such as *Klebsiella pneumoniae* and *Pseudomonas aeruginosa.* The "atypical" organisms include *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella* species as well as respiratory viruses such as influenza viruses, adenoviruses, human metapneumovirus, and respiratory syncytial viruses. Overall, with the increasing use of pneumococcal vaccine, the incidence of pneumococcal pneumonia appears to be decreasing. Cases due to *M. pneumoniae* and *C. pneumoniae*, however, appear to be increasing in incidence, especially among young adults. Viruses may be responsible for a large proportion of CAP cases that require hospital admission, even in adults. Polymerase chain reaction (PCR)–based testing shows that viruses may be present in 20–30% of healthy adults and in the same percentage of patients with pneumonia, including those who are severely ill. The most common of these viruses are influenza, parainfluenza, and respiratory syncytial viruses. Whether they are etiologic pathogens, co-pathogens, or simply colonizers cannot always be determined. Atypical organisms cannot be cultured on standard media or seen on Gram's stain. The frequency and importance of atypical pathogens have significant implications for therapy. They are intrinsically resistant to all β-lactam agents and must be treated with a macrolide, a fluoroquinolone, or a tetracycline. In the ~10–15% of CAP cases that are polymicrobial, the etiology usually includes a combination of typical and atypical pathogens.

TABLE 121-2

Microbial Causes of Community-Acquired Pneumonia, by Site of Care

OUTPATIENTS	HOSPITALIZED PATIENTS	
	NON-ICU	ICU
Streptococcus pneumoniae *Mycoplasma pneumoniae* *Haemophilus influenzae* *C. pneumoniae* Respiratory viruses[a]	*S. pneumoniae* *M. pneumoniae* *Chlamydia pneumoniae* *H. influenzae* *Legionella* spp. Respiratory viruses[a]	*S. pneumoniae* *Staphylococcus aureus* *Legionella* spp. Gram-negative bacilli *H. influenzae* Respiratory viruses

[a]Influenza A and B viruses, human metapneumovirus, adenoviruses, respiratory syncytial viruses, parainfluenza viruses.

Abbreviation: ICU, intensive care unit.

Anaerobes play a significant role only when an episode of aspiration has occurred days to weeks before presentation for pneumonia. The combination of an unprotected airway (e.g., in patients with alcohol or drug overdose or a seizure disorder) and significant gingivitis constitutes the major risk factor. Anaerobic pneumonias are often complicated by abscess formation and by significant empyemas or parapneumonic effusions.

S. aureus pneumonia is well known to complicate influenza infection. However, MRSA has been reported as a primary etiologic agent of CAP. While this entity is still relatively uncommon, clinicians must be aware of its potentially serious consequences, such as necrotizing pneumonia. Two important developments have led to this problem: the spread of MRSA from the hospital setting to the community and the emergence of genetically distinct strains of MRSA in the community. The community-acquired MRSA (CA-MRSA) strains may infect healthy individuals with no association with health care.

Unfortunately, despite a careful history and physical examination as well as routine radiographic studies, the causative pathogen in a case of CAP is difficult to predict with any degree of certainty; in more than one-half of cases, a specific etiology is never determined. Nevertheless, epidemiologic and risk factors may suggest the involvement of certain pathogens (**Table 121-3**).

TABLE 121-3

Epidemiologic Factors Suggesting Possible Causes of Community-Acquired Pneumonia

FACTOR	POSSIBLE PATHOGEN(S)
Alcoholism	*Streptococcus pneumoniae*, oral anaerobes, *Klebsiella pneumoniae*, *Acinetobacter* spp., *Mycobacterium tuberculosis*
COPD and/or smoking	*Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Legionella* spp., *S. pneumoniae*, *Moraxella catarrhalis*, *Chlamydia pneumoniae*
Structural lung disease (e.g., bronchiectasis)	*P. aeruginosa*, *Burkholderia cepacia*, *Staphylococcus aureus*
Dementia, stroke, decreased level of consciousness	Oral anaerobes, gram-negative enteric bacteria
Lung abscess	CA-MRSA, oral anaerobes, endemic fungi, *M. tuberculosis*, atypical mycobacteria
Travel to Ohio or St. Lawrence river valley	*Histoplasma capsulatum*
Travel to southwestern United States	Hantavirus, *Coccidioides* spp.
Travel to Southeast Asia	*Burkholderia pseudomallei*, avian influenza virus
Stay in hotel or on cruise ship in previous 2 weeks	*Legionella* spp.
Local influenza activity	Influenza virus, *S. pneumoniae*, *S. aureus*
Exposure to bats or birds	*H. capsulatum*
Exposure to birds	*Chlamydia psittaci*
Exposure to rabbits	*Francisella tularensis*
Exposure to sheep, goats, parturient cats	*Coxiella burnetii*

Abbreviations: CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus;* COPD, chronic obstructive pulmonary disease.

EPIDEMIOLOGY

More than 5 million CAP cases occur annually in the United States. Along with influenza, CAP is the eighth leading cause of death in this country. Usually, 80% of the affected patients are treated as outpatients and 20% as inpatients. The mortality rate among outpatients is usually <5%, whereas among hospitalized patients the rate can range from ~12% to 40%, depending on whether treatment is provided in or outside of the intensive care unit

(ICU). In the United States, CAP is the number one cause of death from infection among patients >65 years of age. Further compounding its impact is the fact that 18% of hospitalized CAP patients are readmitted within 1 month of discharge. CAP results in more than 1.2 million hospitalizations and more than 55,000 deaths annually. The overall yearly cost associated with CAP is estimated at $17 billion. The incidence rates are highest at the extremes of age. The overall annual rate in the United States is 12 cases/1000 persons, but the figure increases to 12–18/1000 among children <4 years of age and to 20/1000 among persons >60 years of age.

The risk factors for CAP in general and for pneumococcal pneumonia in particular have implications for treatment regimens. Risk factors for CAP include alcoholism, asthma, immunosuppression, institutionalization, and an age of ≥70 years. In the elderly, factors such as decreased cough and gag reflexes as well as reduced antibody and Toll-like receptor responses increase the likelihood of pneumonia. Risk factors for pneumococcal pneumonia include dementia, seizure disorders, heart failure, cerebrovascular disease, alcoholism, tobacco smoking, chronic obstructive pulmonary disease (COPD), and HIV infection. CA-MRSA pneumonia is more likely in patients with skin colonization or infection with CA-MRSA. Enterobacteriaceae tend to infect patients who have recently been hospitalized and/or received antibiotic therapy or who have comorbidities such as alcoholism, heart failure, or renal failure. *P. aeruginosa* is a particular problem in patients with severe structural lung disease, such as bronchiectasis, cystic fibrosis, or severe COPD. Risk factors for *Legionella* infection include diabetes, hematologic malignancy, cancer, severe renal disease, HIV infection, smoking, male gender, and a recent hotel stay or ship cruise.

CLINICAL MANIFESTATIONS

CAP can vary from indolent to fulminant in presentation and from mild to fatal in severity. Manifestations of progression and severity include both constitutional findings and those limited to the lung and associated structures.

The patient is frequently febrile with tachycardia or may have a history of chills and/or sweats. Cough may be either nonproductive or productive of mucoid, purulent, or blood-tinged sputum. Gross hemoptysis is suggestive of CA-MRSA pneumonia. Depending on severity, the patient may be able to speak in full sentences or may be very short of breath. If the pleura is involved, the patient may experience pleuritic chest pain. Up to 20% of patients may have gastrointestinal symptoms such as nausea, vomiting, and/or diarrhea. Other symptoms may include fatigue, headache, myalgias, and arthralgias.

Findings on physical examination vary with the degree of pulmonary consolidation and the presence or absence of a significant pleural effusion. An increased respiratory rate and use of accessory muscles of respiration are common. Palpation may reveal increased or decreased tactile fremitus, and the percussion note can vary from dull to flat, reflecting underlying consolidated lung and pleural fluid, respectively. Crackles, bronchial breath sounds, and possibly a pleural friction rub may be heard on auscultation. The clinical presentation may not be so obvious in the elderly, who may initially display new-onset or worsening confusion and few other manifestations. Severely ill patients may have septic shock and evidence of organ failure.

The risk of cardiac complications secondary to enhanced inflammation and procoagulant activity is increased. These complications include myocardial infarction, congestive heart failure, and arrhythmias, particularly in the elderly. In pneumococcal CAP, the increased risk of acute coronary events may be partially driven by pneumolysis, which increases platelet activation. Up to 90% of acute coronary syndromes occur in the first week after onset of CAP, and the risk of new-onset congestive heart failure in elderly hospitalized CAP patients can extend up to 1 year.

DIAGNOSIS

When confronted with possible CAP, the physician must ask two questions: Is this pneumonia, and, if so, what is the likely etiology? The former question is typically answered by clinical and radiographic methods, whereas the latter requires the aid of laboratory techniques.

Clinical Diagnosis

The differential diagnosis includes both infectious and noninfectious entities such as acute bronchitis, acute exacerbations of chronic bronchitis, heart failure, pulmonary embolism, hypersensitivity pneumonitis, and radiation pneumonitis. The importance of a careful history cannot be overemphasized. For example, known cardiac disease may suggest worsening pulmonary edema, while underlying carcinoma may suggest lung injury secondary to irradiation.

Unfortunately, the sensitivity and specificity of the findings on physical examination are less than ideal, averaging 58% and 67%, respectively. As

mentioned earlier, the elderly may initially present with confusion alone. Therefore, chest radiography is often necessary to differentiate CAP from other conditions. Radiographic findings may include risk factors for increased severity (e.g., cavitation or multilobar involvement). Occasionally, radiographic results suggest an etiologic diagnosis. For example, pneumatoceles suggest infection with *S. aureus*, and an upper-lobe cavitating lesion suggests tuberculosis. CT may be of value in a patient with suspected postobstructive pneumonia caused by a tumor or foreign body or suspected cavitary disease. For outpatients, the clinical and radiologic assessments are usually all that is done before treatment for CAP is started since most laboratory results are not available soon enough to influence initial management significantly. In certain cases, the availability of rapid point-of-care outpatient diagnostic tests can be very important; for example, rapid diagnosis of influenza virus infection can prompt specific anti-influenza drug treatment and secondary prevention.

Etiologic Diagnosis

The etiology of pneumonia usually cannot be determined solely on the basis of clinical presentation. Except for CAP patients admitted to the ICU, no data exist to show that treatment directed at a specific pathogen is statistically superior to empirical therapy. The benefit of establishing a microbial etiology can therefore be questioned, particularly in light of the cost of diagnostic testing. However, a number of reasons can be advanced for attempting an etiologic diagnosis. Identification of an unexpected pathogen allows narrowing of the initial empirical regimen, thereby decreasing antibiotic selection pressure and lessening the risk of resistance. Pathogens with important public safety implications, such as *Mycobacterium tuberculosis* and influenza virus, may be found in some cases. Finally, without culture and susceptibility data, trends in resistance cannot be followed accurately, and appropriate empirical therapeutic regimens are harder to devise.

Gram's Stain and Culture of Sputum

The main purpose of the sputum Gram's stain is to ensure that a sample is suitable for culture. However, Gram's staining may also identify certain pathogens (e.g., *S. pneumoniae*, *S. aureus*, and gram-negative bacteria) by their characteristic appearance. To be adequate for culture, a sputum sample must have >25 neutrophils and <10 squamous epithelial cells per low-power field. The sensitivity and specificity of the sputum Gram's stain and culture are highly variable. Even in cases of proven bacteremic pneumococcal pneumonia, the yield of positive cultures from sputum samples is ≤50%.

Many patients, particularly elderly individuals, may not be able to produce an appropriate expectorated sputum sample. Others may already have started a course of antibiotics that can interfere with culture results at the time a sample is obtained. Inability to produce sputum can result from dehydration, and its correction may result in increased sputum production and a more obvious infiltrate on chest radiography. For patients admitted to the ICU and intubated, a deep-suction aspirate or bronchoalveolar lavage sample (obtained either via bronchoscopy or non-bronchoscopically) has a high yield on culture when sent to the microbiology laboratory as soon as possible. Since the etiologies in severe CAP are somewhat different from those in milder disease (Table 121-2), the greatest benefit of staining and culturing respiratory secretions is to alert the physician of unsuspected and/or resistant pathogens and to permit appropriate modification of therapy. Other stains and cultures (e.g., specific stains for *M. tuberculosis* or fungi) may be useful as well.

Blood Cultures

The yield from blood cultures, even when samples are collected before antibiotic therapy, is disappointingly low. Only 5–14% of cultures of blood from patients hospitalized with CAP are positive, and the most frequently isolated pathogen is *S. pneumoniae.* Since recommended empirical regimens all provide pneumococcal coverage, a blood culture positive for this pathogen has little, if any, effect on clinical outcome. However, susceptibility data may allow narrowing of antibiotic therapy in appropriate cases. Because of the low yield and the lack of significant impact on outcome, blood cultures are no longer considered *de rigueur* for all hospitalized CAP patients. Certain high-risk patients—including those with neutropenia secondary to pneumonia, asplenia, complement deficiencies, chronic liver disease, or severe CAP—should have blood cultured.

Urinary Antigen Tests

Two commercially available tests detect pneumococcal and *Legionella* antigen in urine. The test for *Legionella pneumophila* detects only serogroup 1, but this serogroup accounts for most community-acquired cases of Legionnaires' disease in the United States. The sensitivity and specificity of the *Legionella* urine antigen test are as high as 70% and 99%, respectively. The pneumococcal urine antigen test is also quite sensitive and specific (70% and >90%, respectively). Although false-positive results can be obtained with samples from pneumococcus-colonized children, the test is generally reliable. Both tests can detect antigen even after the initiation of appropriate antibiotic therapy.

Polymerase Chain Reaction

PCR tests, which amplify a microorganism's DNA or RNA, are available for a number of pathogens. PCR of nasopharyngeal swabs, for example, has become the standard for diagnosis of respiratory viral infection. In addition, PCR can detect the nucleic acid of *Legionella* species, *M. pneumoniae*, *C. pneumoniae*, and mycobacteria. The cost-effectiveness of PCR testing, however, has not been definitively established. In patients with pneumococcal pneumonia, an increased bacterial load documented in whole blood by PCR is associated with an increased risk of septic shock, the need for mechanical ventilation, and death. Clinical availability of such a test could conceivably help identify patients suitable for ICU admission.

Serology

A fourfold rise in specific IgM antibody titer between acute- and convalescent-phase serum samples is generally considered diagnostic of infection with the pathogen in question. In the past, serologic tests were used to help identify atypical pathogens as well as selected unusual organisms such as *Coxiella burnetii.* Recently, however, they have fallen out of favor because of the time required to obtain a final result for the convalescent-phase sample and the difficulty of interpretation.

Biomarkers

A number of substances can serve as markers of severe inflammation. The two most commonly in use are C-reactive protein (CRP) and procalcitonin (PCT). Levels of these acute-phase reactants increase in the presence of an inflammatory response, particularly to bacterial pathogens. CRP may be of use in the identification of worsening disease or treatment failure, and PCT may play a role in distinguishing bacterial from viral infection, determining the need for antibacterial therapy, or deciding when to discontinue treatment. PCT testing can result in less antibiotic use in CAP with no concomitant increase in treatment failure or mortality risk. These tests should not be used on their own, but, when interpreted in conjunction with other findings from the history, physical examination, radiology, and laboratory tests, may help with antibiotic stewardship and appropriate management of seriously ill patients with CAP.

TREATMENT

TREATMENT

Community-Acquired Pneumonia

SITE OF CARE

The cost of inpatient management exceeds that of outpatient treatment by a factor of 20, and hospitalization accounts for most CAP-related expenditures. Thus the decision to hospitalize a patient with CAP has considerable implications, and late admission to the ICU is associated with increased mortality risk. Certain patients can be managed at home, and others clearly require treatment in the hospital, but the choice is sometimes difficult. Tools that objectively assess the risk of adverse outcomes, including severe illness and death, can minimize unnecessary hospital admissions. Although a number of prediction rules exist, the two most frequently used are the Pneumonia Severity Index (PSI), a prognostic model used to identify patients at low risk of dying, and the CURB-65 criteria, a severity-of-illness score.

To determine the PSI, points are given for 20 variables, including age, coexisting illness, and abnormal physical and laboratory findings. On the basis of the resulting score, patients are assigned to one of five classes with the following mortality rates: class 1, 0.1%; class 2, 0.6%; class 3, 2.8%; class 4, 8.2%; and class 5, 29.2%. Determination of the PSI is often impractical in a busy emergency-department setting because of the number of variables. However, clinical trials demonstrate that routine use of the PSI results in lower admission rates for class 1 and class 2 patients. Patients in class 3 could ideally be admitted to an observation unit until a further decision can be made.

The CURB-65 criteria include five variables: confusion (C); urea >7 mmol/L (U); respiratory rate ≥30/min (R); blood pressure, systolic ≤90 mmHg or diastolic ≤60 mmHg (B); and age ≥65 years. Patients with a score of 0, among whom the 30-day mortality rate is 1.5%, can be treated outside the hospital. With a score of 1 or 2, the patient should be hospitalized unless the score is entirely or in part attributable to an age of ≥65 years. In such cases, hospitalization may not be necessary. Among patients with scores of ≥3, mortality rates are 22% overall; these patients may require ICU admission.

It is not clear which assessment tool is superior. Whichever system is used, these objective criteria must always be tempered by careful consideration of factors relevant to individual patients, including the ability to comply reliably with an oral antibiotic regimen and the resources available to the patient outside the hospital.

Neither PSI nor CURB-65 is accurate in determining the need for ICU admission. Septic shock or respiratory failure in the emergency department is an obvious indication for ICU care. However, mortality rates are higher among less ill patients who are admitted to the floor and then deteriorate than among equally ill patients monitored in the ICU. A variety of scores have been proposed to identify patients most likely to have early deterioration **(Table 121-4)**. Most factors in these scores are similar to the minor severity criteria proposed by the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) in their guidelines for the management of CAP. Recent data suggest that thrombocytopenia, leukopenia, and hypothermia can be removed from the list of minor criteria.

ANTIBIOTIC RESISTANCE

Antimicrobial resistance is a significant problem that threatens to diminish our therapeutic armamentarium. Misuse of antibiotics results in increased antibiotic selection pressure that can affect resistance locally and globally by clonal dissemination. For CAP, the main resistance issues currently involve *S. pneumoniae* and CA-MRSA.

S. pneumoniae

In general, pneumococcal resistance is acquired by direct DNA incorporation and remodeling resulting from contact with closely related oral commensal bacteria, by the process of natural transformation, or by mutation of certain genes.

The minimal inhibitory concentration (MIC) cutoffs for penicillin in pneumonia are ≤2 µg/mL for susceptible, >2–4 µg/mL for intermediate, and ≥8 µg/mL for resistant. A change in susceptibility thresholds resulted in a dramatic decrease in the proportion of pneumococcal isolates considered nonsusceptible. For meningitis, MIC thresholds remain at the former higher levels. Fortunately, resistance to penicillin appeared to plateau even before the change in MIC thresholds. Pneumococcal resistance to β-lactam drugs is due solely to low-affinity penicillin-binding proteins. Risk factors for penicillin-resistant pneumococcal infection include recent antimicrobial therapy, an age of <2 years or >65 years, attendance at day-care centers, recent hospitalization, and HIV infection.


In contrast to penicillin resistance, resistance to macrolides is increasing through several mechanisms. *Target-site modification* caused by ribosomal methylation in 23S rRNA encoded by the *ermB* gene results in high-level resistance (MICs, ≥64 µg/mL) to macrolides, lincosamides, and streptogramin B–type antibiotics. The *efflux mechanism* encoded by the *mef* gene (*M phenotype*) is usually associated with low-level resistance (MICs, 1–32 µg/mL). These two mechanisms account for ~45% and ~65%, respectively, of resistant pneumococcal isolates in the United States. High-level resistance to macrolides is more common in Europe, whereas lower-level resistance predominates in North America. In some countries, including the United States, the prevalence of macrolide-resistant *S. pneumoniae* exceeds 25%. In such situations, a macrolide should not be used as empirical monotherapy.

Pneumococcal resistance to fluoroquinolones (e.g., ciprofloxacin and levofloxacin) has been reported. Changes can occur in one or both target sites (topoisomerases II and IV) from mutations in the *gyrA* and *parC* genes, respectively. In addition, an efflux pump may play a role in pneumococcal resistance to fluoroquinolones.

Isolates resistant to drugs from three or more antimicrobial classes with different mechanisms of action are considered MDR strains. The propensity for an association of pneumococcal resistance to penicillin with reduced susceptibility to other drugs, such as macrolides, tetracyclines, and trimethoprim-sulfamethoxazole, is also of concern. In the United States, 58.9% of penicillin-resistant pneumococcal isolates from blood are also resistant to macrolides.

The most important risk factor for antibiotic-resistant pneumococcal infection is use of a specific antibiotic within the previous 3 months. Therefore, a patient's history of prior antibiotic treatment is a critical factor in avoiding the use of an inappropriate antibiotic.

M. pneumoniae

Macrolide-resistant *M. pneumoniae* has been reported in a number of countries, including Germany (3%), Japan (30%), China (95%), and France and the United States (5–13%). *Mycoplasma* resistance to macrolides is on the rise as a result of binding-site mutation in domain V of 23S rRNA.

CA-MRSA

CAP due to MRSA may be caused by the classic hospital-acquired strains or by genotypically and phenotypically distinct community-acquired strains. Most infections with the former strains have been acquired either directly or indirectly by contact with the health care environment (Table 121-1). However, in some hospitals, CA-MRSA strains are displacing the classic hospital-acquired strains—a trend suggesting that the newer strains may be more robust and blurring this distinction.


Methicillin resistance in *S. aureus* is determined by the *mecA* gene, which encodes for resistance to all β-lactam drugs. At least five *staphylococcal chromosomal cassette mec* (*SCCmec*) types have been described. The typical hospital-acquired strain usually has type II or III, whereas CA-MRSA has a type IV SCC*mec* element. CA-MRSA isolates tend to be less resistant than the older hospital-acquired strains and are often susceptible to trimethoprim-sulfamethoxazole, clindamycin, and tetracycline in addition to vancomycin and linezolid. However, the most important distinction is that CA-MRSA strains also carry genes for superantigens, such as enterotoxins B and C and Panton-Valentine leukocidin, a membrane-tropic toxin that can create cytolytic pores in polymorphonuclear neutrophils, monocytes, and macrophages.

Gram-Negative Bacilli

A detailed discussion of resistance among gram-negative bacilli is beyond the scope of this chapter **(see Chap. 156)**. Fluoroquinolone resistance among isolates of *Escherichia coli* from the community appears to be increasing. *Enterobacter* species are typically resistant to cephalosporins; the drugs of choice for use against these bacteria are usually fluoroquinolones or carbapenems. Similarly, when infections due to bacteria producing extended-spectrum β-lactamases are documented or suspected, a fluoroquinolone or a carbapenem should be used.

INITIAL ANTIBIOTIC MANAGEMENT

Since the etiology of CAP is rarely known at the outset of treatment, initial therapy is usually empirical, designed to cover the most likely pathogens (Table 121-2). In all cases, antibiotic treatment should be initiated as expeditiously as possible. The CAP treatment guidelines in the United States (summarized in **Table 121-5**) represent joint statements from the IDSA and the ATS; the Canadian guidelines come from the Canadian Infectious Disease Society and the Canadian Thoracic Society. In these guidelines, coverage is always provided for the pneumococcus and atypical pathogens. In contrast, guidelines from some European countries do not always include atypical coverage based on local epidemiologic data. The U.S./Canadian approach is supported by retrospective data derived from administrative databases including thousands of patients. Atypical pathogen coverage provided by the addition of a macrolide to a β-lactam or by the use of a fluoroquinolone alone has been consistently associated with a significant reduction in mortality rates compared with those for β-lactam coverage alone.

For the treatment of severe CAP, accumulating data continue to demonstrate the benefits of including a macrolide, such as reduced mortality. However, two recent studies of patients hospitalized with moderate CAP yielded differing results. One study demonstrated a more rapid return to clinical stability and fewer adverse events with a β-lactam–macrolide combination than with a β-lactam alone. Using cluster randomization, the second study reported no difference among three regimens—a β-lactam alone, a β-lactam–macrolide combination, and a fluoroquinolone—but had significant design flaws, including a lack of chest radiographic confirmation in 24% of cases and significant rates of noncompliance with the assigned regimen.

Empirical treatment regimens for CAP are listed in Table 121-5. In general, the recommendations in the IDSA/ATS guidelines published in 2007 continue to apply but with a possible exception for treatment of outpatients who have previously been well and have not received an antibiotic within 3 months. Given the rise of macrolide resistance among pneumococci, consideration of local epidemiologic and susceptibility data as well as the patient's recent use of any antibiotics is imperative before selection of a regimen, particularly as regards macrolide monotherapy. If concern exists about macrolide resistance, the patient is otherwise well and has not recently received antibiotics, and the local doxycycline resistance rate among pneumococcal isolates is <25%, doxycycline may be used instead of macrolide monotherapy. Otherwise, a fluoroquinolone or a β-lactam plus a macrolide should be used.

A meta-analysis found ceftaroline to be superior to ceftriaxone as the β-lactam component of IV empirical treatment of CAP in hospitalized patients in PORT risk class III or IV who have not received prior antibiotics. Clinical response rates for patients infected with *S. pneumoniae* or *S. aureus* also favored ceftaroline. Patients who had documented or suspected infection due to *P. aeruginosa* were excluded.

Once the etiologic agent(s) and their susceptibilities are known, therapy may be altered to target the specific pathogen(s). However, this decision is not always straightforward. If blood cultures yield *S. pneumoniae* sensitive to penicillin after 2 days of treatment with a macrolide plus a β-lactam or

with a fluoroquinolone alone, should therapy be switched to penicillin alone? The concern here is that a β-lactam alone would not be effective in the potential 15% of cases with atypical co-infection. No standard approach exists. Some experts think that 3 days of macrolide therapy is adequate for *Mycoplasma* infection and that, unless the test for *Legionella* urinary antigen is positive, treatment can be continued with a β-lactam alone. In all cases, the individual patient and the various risk factors must be considered.

Management of bacteremic pneumococcal pneumonia is also controversial. Data from nonrandomized studies suggest that combination therapy (especially with a β-lactam–macrolide combination) is associated with a lower mortality rate than monotherapy, particularly in severely ill patients. The exact reason is unknown, but possible explanations include an additive or synergistic antibacterial effect, antimicrobial tolerance, atypical co-infection, or the immunomodulatory effects of the macrolides.

For CAP patients admitted to the ICU, the risk of infection with *P. aeruginosa* or CA-MRSA is increased. Empirical coverage should be considered when a patient has risk factors or a Gram's stain suggestive of these pathogens (Table 121-5). If CA-MRSA is suspected, either linezolid or vancomycin—with or without clindamycin to inhibit toxin production—can be added to the initial empirical regimen. There is increasing concern about vancomycin's loss of potency against MRSA, poor penetration into epithelial lining fluid, and lack of effect on toxin production relative to linezolid.

Although hospitalized patients have traditionally received initial therapy by the IV route, some drugs—particularly the fluoroquinolones—are very well absorbed and can be given orally from the outset to certain patients. For patients initially treated IV, a switch to oral treatment is appropriate as long as the patient can ingest and absorb the drugs, is hemodynamically stable, and is showing clinical improvement.

The duration of treatment for CAP has generated considerable interest. Studies with fluoroquinolones and telithromycin suggest that a 5-day course is sufficient for otherwise uncomplicated CAP but a longer course may be required for patients with bacteremia, metastatic infection, or infection with a virulent pathogen such as *P. aeruginosa* or CA-MRSA.

ADJUNCTIVE MEASURES

In addition to appropriate antimicrobial therapy, certain adjunctive measures should be used. Adequate hydration, oxygen therapy for hypoxemia, vasopressors, and assisted ventilation when necessary are critical to successful treatment. Randomized placebo-controlled trials have shown a benefit in treatment of hospitalized patients and patients who have severe CAP with prednisone and methylprednisolone, respectively. The value of adjunctive therapy with agents such as statins and angiotensin-converting enzyme inhibitors remains unproven in the management of CAP.

FAILURE TO IMPROVE

Patients slow to respond to therapy should be reevaluated at about day 3 (sooner if their condition is worsening rather than simply not improving), and several possible scenarios should be considered. A number of noninfectious conditions mimic pneumonia, including pulmonary edema, pulmonary embolism, lung carcinoma, radiation and hypersensitivity pneumonitis, and connective tissue disease involving the lungs. If the patient truly has CAP and empirical treatment is aimed at the correct pathogen, lack of response may be explained in a number of ways. The pathogen may be resistant to the drug selected, or a sequestered focus (e.g., lung abscess or empyema) may be blocking access of the antibiotic(s) to the pathogen. The patient may be getting either the wrong drug or the correct drug at the wrong dose or frequency of administration. Another possibility is that CAP is the correct diagnosis but an unsuspected pathogen (e.g., CA-MRSA, *M. tuberculosis*, or a fungus) is the cause. Nosocomial superinfections—both pulmonary and extrapulmonary—are other possible explanations for a hospitalized patient's failure to improve or deterioration. In all cases of delayed response or worsening condition, the patient must be carefully reassessed and appropriate studies initiated, possibly including procedures such as CT or bronchoscopy.

COMPLICATIONS

Complications of severe CAP include respiratory failure, shock and multiorgan failure, coagulopathy, and exacerbation of comorbid illnesses. Three particularly noteworthy conditions are metastatic infection, lung abscess, and complicated pleural effusion. Metastatic infection (e.g., brain abscess or endocarditis) is very unusual and will require a high degree of suspicion and a detailed workup for proper treatment. Lung abscess may occur in association with aspiration or with infection caused by a single CAP pathogen, such as CA-MRSA, *P. aeruginosa*, or (rarely) *S. pneumoniae.* Aspiration pneumonia is typically a polymicrobial infection involving both aerobes and anaerobes. A significant pleural effusion should be tapped for both diagnostic and therapeutic purposes. If the fluid has a pH of <7, a glucose level of <2.2 mmol/L, and a lactate dehydrogenase concentration of >1000 U/L or if bacteria are seen or cultured, it should be completely drained; a chest tube is often required, and video-assisted thoracoscopy may be needed for late treatment or difficult cases.

FOLLOW-UP

Fever and leukocytosis usually resolve within 2–4 days in otherwise healthy patients with CAP, but physical findings may persist longer. Chest radiographic abnormalities are slowest to resolve (4–12 weeks), with the speed of clearance depending on the patient's age and underlying lung disease. Patients may be discharged from the hospital once their clinical conditions, including comorbidities, are stable. The site of residence after discharge (nursing home, home with family, home alone) is an important discharge consideration, particularly for elderly patients. For a hospitalized patient, a follow-up radiograph ~4–6 weeks later is recommended. If relapse or recurrence is documented, particularly in the same lung segment, the possibility of an underlying neoplasm must be considered.

TABLE 121-4

Risk Factors for Early Deterioration in Community-Acquired Pneumonia

Multilobar infiltrates	Hypoalbuminemia
Severe hypoxemia (arterial saturation <90%)	Neutropenia
Severe acidosis (pH <7.30)	Thrombocytopenia
Mental confusion	Hyponatremia
Severe tachypnea (>30 breaths/min)	Hypoglycemia

TABLE 121-5

Empirical Antibiotic Treatment of Community-Acquired Pneumonia

Outpatients
1. Previously healthy and no antibiotics in past 3 months ○ A macrolide [clarithromycin (500 mg PO bid) or azithromycin (500 mg PO once, then 250 mg qd)] *or* ○ Doxycycline (100 mg PO bid) 2. Comorbidities or antibiotics in past 3 months: select an alternative from a different class ○ A respiratory fluoroquinolone [moxifloxacin (400 mg PO qd), gemifloxacin (320 mg PO qd), levofloxacin (750 mg PO qd)] *or* ○ A β-lactam [preferred: high-dose amoxicillin (1 g tid) or amoxicillin/clavulanate (2 g bid); alternatives: ceftriaxone (1–2 g IV qd), cefpodoxime (200 mg PO bid), or cefuroxime (500 mg PO bid)] *plus* a macrolide[a] 3. In regions with a high rate of "high-level" pneumococcal macrolide resistance,[b] consider alternatives listed above for patients with comorbidities.
Inpatients, Non-ICU
• A respiratory fluoroquinolone [e.g., moxifloxacin (400 mg PO or IV qd) or levofloxacin (750 mg PO or IV qd)] • A β-lactam[c] [e.g., ceftriaxone (1–2 g IV qd), ampicillin (1–2 g IV q4–6h), cefotaxime (1–2 g IV q8h), ertapenem (1 g IV qd)] *plus* a macrolide[d] [e.g., oral clarithromycin or azithromycin as listed above or IV azithromycin (1 g once, then 500 mg qd)]
Inpatients, ICU
• A β-lactam[e] [e.g., ceftriaxone (2 g IV qd), ampicillin-sulbactam (2 g IV q8h), or cefotaxime (1–2 g IV q8h)] *plus* either azithromycin or a fluoroquinolone (as listed above for inpatients, non-ICU)
Special Concerns
If Pseudomonas is a consideration: • An antipseudomonal β-lactam [e.g., piperacillin/tazobactam (4.5 g IV q6h), cefepime (1–2 g IV q12h), imipenem (500 mg IV q6h), meropenem (1 g IV q8h)] *plus* either ciprofloxacin (400 mg IV q12h) or levofloxacin (750 mg IV qd) • The above β-lactams *plus* an aminoglycoside [amikacin (15 mg/kg qd) or tobramycin (1.7 mg/kg qd)] *plus* azithromycin • The above β-lactams[f] *plus* an aminoglycoside *plus* an antipneumococcal fluoroquinolone *If CA-MRSA is a consideration:* • Add linezolid (600 mg IV q12h) or vancomycin (15 mg/kg q12h initially, with adjusted doses) *plus* clindamycin (300 mg q6h)

[a]Doxycycline (100 mg PO bid) is an alternative to the macrolide. [b]MICs >16 μg/mL in 25% of isolates. [c]A respiratory fluoroquinolone should be used for penicillin-allergic patients. [d]Doxycycline (100 mg IV q12h) is an alternative to the macrolide. [e]For penicillin-allergic patients, use a respiratory fluoroquinolone and aztreonam (2 g IV q8h). [f]For penicillin-allergic patients, substitute aztreonam.

Abbreviations: CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus;* ICU, intensive care unit.

PROGNOSIS

The prognosis of CAP depends on the patient's age, comorbidities, and site of treatment (inpatient or outpatient). Young patients without comorbidity do well and usually recover fully after ~2 weeks. Older patients and those with comorbid conditions can take several weeks longer to recover fully. The

overall mortality rate for the outpatient group is <5%. For patients requiring hospitalization, the overall mortality rate ranges from 2 to 40%, depending on the category of patient and the processes of care, particularly the administration of appropriate antibiotics as soon as possible.

PREVENTION

The main preventive measure is vaccination **(Chap. 118)**. Recommendations of the Advisory Committee on Immunization Practices should be followed for influenza and pneumococcal vaccines.

A pneumococcal polysaccharide vaccine (PPSV23) and a protein conjugate pneumococcal vaccine (PCV13) are available in the United States **(Chap. 141)**. The former product contains capsular material from 23 pneumococcal serotypes; in the latter, capsular polysaccharide from 13 of the most common pneumococcal pathogens affecting children is linked to an immunogenic protein. PCV13 produces T cell–dependent antigens that result in long-term immunologic memory. Administration of this vaccine to children has led to an overall decrease in the prevalence of antimicrobial-resistant pneumococci and in the incidence of invasive pneumococcal disease among both children and adults. However, vaccination can be followed by the replacement of vaccine serotypes with nonvaccine serotypes, as was seen with serotypes 19A and 35B after introduction of the original 7-valent conjugate vaccine. PCV13 is also recommended for the elderly and for younger immunocompromised patients. Because of an increased risk of pneumococcal infection, even among patients without obstructive lung disease, smokers should be strongly encouraged to stop smoking.

The influenza vaccine is available in an inactivated or recombinant form. The live attenuated influenza vaccine or “nasal spray” vaccine is no longer recommended. In the event of an influenza outbreak, unprotected patients at risk from complications should be vaccinated immediately and given chemoprophylaxis with either oseltamivir or zanamivir for 2 weeks—i.e., until vaccine-induced antibody levels are sufficiently high.

VENTILATOR-ASSOCIATED PNEUMONIA

Most research on hospital-acquired pneumonia has focused on VAP. However, the information and principles based on this research can be applied to non-ICU HAP as well. The greatest difference between VAP and HAP studies is the dependence on expectorated sputum for a microbiologic diagnosis of HAP (as for that of CAP), which is further complicated by frequent colonization by pathogens in patients with HAP. Therefore, most of the literature has focused on HAP resulting in intubation, where, once again, access to the lower respiratory tract facilitates an etiologic diagnosis.

ETIOLOGY

Potential etiologic agents of VAP include both MDR and non-MDR bacterial pathogens **(Table 121-6)**. The non-MDR group is nearly identical to the pathogens found in severe CAP (Table 121-2); it is not surprising that such pathogens predominate if VAP develops in the first 5–7 days of the hospital stay. However, if patients have other risk factors, MDR pathogens are a consideration, even early in the hospital course. The relative frequency of individual MDR pathogens can vary significantly from hospital to hospital and even between different critical care units within the same institution. Most hospitals have problems with *P. aeruginosa* and MRSA, but other MDR pathogens are often institution-specific. Less commonly, fungal and viral pathogens cause VAP, usually affecting severely immunocompromised patients. Rarely, community-associated viruses cause mini-epidemics, usually when introduced by ill health care workers.

TABLE 121-6

Microbiologic Causes of Ventilator-Associated Pneumonia

NON-MDR PATHOGENS	MDR PATHOGENS
Streptococcus pneumoniae	*Pseudomonas aeruginosa*
Other *Streptococcus* spp.	Methicillin-resistant *S. aureus*
Haemophilus influenzae	*Acinetobacter* spp.
Methicillin-sensitive *Staphylococcus aureus*	Antibiotic-resistant Enterobacteriaceae
Antibiotic-sensitive Enterobacteriaceae	ESBL-positive strains
Escherichia coli	Carbapenem-resistant strains
Klebsiella pneumoniae	*Legionella pneumophila*
Proteus spp.	*Burkholderia cepacia*
Enterobacter spp.	*Aspergillus* spp.
Serratia marcescens	

Abbreviations: ESBL, extended-spectrum β-lactamase; MDR, multidrug-resistant.

EPIDEMIOLOGY

Pneumonia is a common complication among patients requiring mechanical ventilation. Prevalence estimates vary between 6 and 52 cases per 100 patients, depending on the population studied. On any given day in the ICU, an average of 10% of patients will have pneumonia—VAP in the overwhelming majority of cases. The frequency of diagnosis is not static but changes with the duration of mechanical ventilation, with the highest hazard ratio in the first 5 days and a plateau in additional cases (1% per day) after ~2 weeks. However, the cumulative rate among patients who remain ventilated for as long as 30 days is as high as 70%. These rates often do not reflect the recurrence of VAP in the same patient. Once a ventilated patient is transferred to a chronic-care facility or to home, the incidence of pneumonia drops significantly, especially in the absence of other risk factors for pneumonia. However, in chronic ventilator units, purulent tracheobronchitis becomes a significant issue, often interfering with efforts to wean patients off mechanical ventilation (**Chap. 295**).

Three factors are critical in the pathogenesis of VAP: colonization of the oropharynx with pathogenic microorganisms, aspiration of these organisms from the oropharynx into the lower respiratory tract, and compromise of the normal host defense mechanisms. Most risk factors and their corresponding prevention strategies pertain to one of these three factors (**Table 121-7**).

TABLE 121-7

Pathogenic Mechanisms and Corresponding Prevention Strategies for Ventilator-Associated Pneumonia

PATHOGENIC MECHANISM	PREVENTION STRATEGY
Oropharyngeal colonization with pathogenic bacteria	
Elimination of normal flora	Avoidance of prolonged antibiotic courses
Large-volume oropharyngeal aspiration around time of intubation	Short course of prophylactic antibiotics for comatose patients[a]
Gastroesophageal reflux	Postpyloric enteral feeding[b]; avoidance of high gastric residuals, prokinetic agents
Bacterial overgrowth of stomach	Avoidance of prophylactic agents that raise gastric pH[b]; selective decontamination of digestive tract with nonabsorbable antibiotics[b]
Cross-infection from other colonized patients	Hand washing, especially with alcohol-based hand rub; intensive infection control education[a]; isolation; proper cleaning of reusable equipment
Large-volume aspiration	Endotracheal intubation; rapid-sequence intubation technique; avoidance of sedation; decompression of small-bowel obstruction
Microaspiration around endotracheal tube	
Endotracheal intubation	Noninvasive ventilation[a]
Prolonged duration of ventilation	Daily awakening from sedation,[a] weaning protocols[a]
Abnormal swallowing function	Early percutaneous tracheostomy[a]
Secretions pooled above endotracheal tube	Head of bed elevated[a]; continuous aspiration of subglottic secretions with specialized endotracheal tube[a]; avoidance of reintubation; minimization of sedation and patient transport
Altered lower respiratory host defenses	Tight glycemic control[b]; lowering of hemoglobin transfusion threshold

[a]Strategies demonstrated to be effective in at least one randomized controlled trial. [b]Strategies with negative randomized trials or conflicting results.

The most obvious risk factor is the endotracheal tube, which bypasses the normal mechanical factors preventing aspiration. While the presence of an endotracheal tube may prevent large-volume aspiration, microaspiration is actually exacerbated by secretions pooling above the cuff. The endotracheal tube and the concomitant need for suctioning can damage the tracheal mucosa, thereby facilitating tracheal colonization. In addition, pathogenic bacteria can form a glycocalyx biofilm on the tube's surface that protects them from both antibiotics and host defenses. The bacteria can also be dislodged during suctioning and can reinoculate the trachea, or tiny fragments of glycocalyx can embolize to distal airways, carrying bacteria with them.

In a high percentage of critically ill patients, the normal oropharyngeal flora is replaced by pathogenic microorganisms. The most important risk

factors are antibiotic selection pressure, cross-infection from other infected/colonized patients or contaminated equipment, and malnutrition. Of these factors, antibiotic exposure poses the greatest risk by far. Pathogens such as *P. aeruginosa* almost never cause infection in patients without prior exposure to antibiotics. The recent emphasis on hand hygiene has lowered the cross-infection rate.

How the lower respiratory tract defenses become overwhelmed remains poorly understood. Almost all intubated patients experience microaspiration and are at least transiently colonized with pathogenic bacteria. However, only around one-third of colonized patients develop VAP. Colony counts increase to high levels, sometimes days before the development of clinical pneumonia; these increases suggest that the final step in VAP development, independent of aspiration and oropharyngeal colonization, is the overwhelming of host defenses. Severely ill patients with sepsis and trauma appear to enter a state of immunoparalysis several days after admission to the ICU—a time that corresponds to the greatest risk of developing VAP. The mechanism of this immunosuppression is not clear, although several factors have been suggested. Hyperglycemia and more frequent transfusions adversely affect the immune response.

CLINICAL MANIFESTATIONS

The clinical manifestations are generally the same in VAP as in all other forms of pneumonia: fever, leukocytosis, increase in respiratory secretions, and pulmonary consolidation on physical examination, along with a new or changing radiographic infiltrate. The frequency of abnormal chest radiographs before the onset of pneumonia in intubated patients and the limitations of portable radiographic technique make interpretation of radiographs more difficult than in patients who are not intubated. Other clinical features may include tachypnea, tachycardia, worsening oxygenation, and increased minute ventilation.

DIAGNOSIS

No single set of criteria is reliably diagnostic of pneumonia in a ventilated patient. The inability to accurately identify such patients compromises efforts to prevent and treat VAP and even calls into question estimates of the impact of VAP on mortality rates.

Application of the clinical criteria typical for CAP consistently results in overdiagnosis of VAP, largely because of three common findings in at-risk patients: (1) frequent tracheal colonization with pathogenic bacteria in patients with endotracheal tubes, (2) multiple alternative causes of radiographic infiltrates in mechanically ventilated patients, and (3) the high frequency of other sources of fever in critically ill patients. The differential diagnosis of VAP includes a number of entities such as atypical pulmonary edema, pulmonary contusion, alveolar hemorrhage, hypersensitivity pneumonitis, acute respiratory distress syndrome, and pulmonary embolism. Clinical findings in ventilated patients with fever and/or leukocytosis may have alternative causes, including antibiotic-associated diarrhea, central line–associated infection, sinusitis, urinary tract infection, pancreatitis, and drug fever. Conditions mimicking pneumonia are often documented in patients in whom VAP has been ruled out by accurate diagnostic techniques. Most of these alternative diagnoses do not require antibiotic treatment; require antibiotics different from those used to treat VAP; or require some additional intervention, such as surgical drainage or catheter removal, for optimal management.

This diagnostic dilemma has led to debate and controversy. The major question is whether a quantitative-culture approach as a means of eliminating false-positive clinical diagnoses is superior to the clinical approach enhanced by principles learned from quantitative-culture studies. The most recent IDSA/ATS guidelines for HAP/VAP gave a weak recommendation for the clinical approach based on availability of resources, cost, and availability of expertise. The guidelines did acknowledge that the use of a quantitative approach may result in less antibiotic use, which may be critical for antibiotic stewardship in the ICU. Therefore, the approach at each institution, or potentially for each patient, should balance the frequency of complex illnesses that are associated with (1) greater frequency of alternative causes of the clinical manifestations, (2) higher colonization rates, and (3) more frequent prior antibiotic therapy versus availability and expertise of invasive techniques with quantitative cultures.

Quantitative-Culture Approach

The essence of the quantitative-culture approach is discrimination between colonization and true infection through determination of the bacterial burden. The more distal in the respiratory tree the diagnostic sampling, the more specific the results and therefore the lower the threshold of growth necessary to diagnose pneumonia and exclude colonization. For example, a quantitative endotracheal aspirate yields proximate samples, and the diagnostic threshold is 10^6 cfu/mL. The protected specimen brush method, in contrast, obtains distal samples and has a threshold of 10^3 cfu/mL. Conversely, sensitivity declines as more distal secretions are obtained, especially when they are collected blindly (i.e., by a technique other than bronchoscopy). Additional tests that may increase the diagnostic yield include Gram's staining, differential cell counts, staining for intracellular

organisms, and detection of local protein levels elevated in response to infection.

The key piece of a quantitative-culture approach is to base subsequent antibiotic therapy on the results of the quantitative cultures. In a study comparing the quantitative with the clinical approach, the use of bronchoscopic quantitative cultures resulted in significantly less antibiotic use at 14 days after study entry, a lower 14-day mortality rate, and a lower 28-day severity-adjusted mortality rate. In addition, more alternative sites of infection were found in patients randomized to the quantitative-culture strategy. A critical aspect of this study was that antibiotic treatment was initiated only in patients whose gram-stained respiratory sample was positive or who displayed signs of hemodynamic instability. Fewer than half as many patients were treated for pneumonia in the bronchoscopy group, and only one-third as many microorganisms were cultured. Other randomized trials of the quantitative-culture approach did not closely link antibiotic management with the results of cultures; thus the validity of their results was compromised.

The Achilles heel of the quantitative approach is the effect of antibiotic therapy. With sensitive microorganisms, a single antibiotic dose can reduce colony counts below the diagnostic threshold. Recent changes in antibiotic therapy are the most significant. After 3 days, the operating characteristics of the tests improve to the point at which they are equivalent to results when no prior antibiotic therapy has been given. Conversely, colony counts above the diagnostic threshold during antibiotic therapy suggest that the current antibiotics are ineffective. Even the normal host response may be sufficient to reduce quantitative-culture counts below the diagnostic threshold if sampling is delayed. In short, expertise in quantitative-culture techniques is critical, with a specimen obtained as soon as pneumonia is suspected and before antibiotic therapy is initiated or changed.

Clinical Approach

General knowledge of the lack of specificity of a clinical diagnosis of VAP and results from invasive quantitative-culture studies have actually improved the clinical approach to the diagnosis of VAP. Tracheal aspirates generally yield at least twice as many potential pathogens as quantitative cultures. However, the causative pathogen is almost always present. The absence of bacteria in gram-stained endotracheal aspirates makes pneumonia an unlikely cause of fever or pulmonary infiltrates. These findings, coupled with a heightened awareness of the alternative diagnoses possible in patients with suspected VAP, can prevent inappropriate overtreatment for pneumonia. Furthermore, the absence of an MDR pathogen in tracheal aspirate cultures eliminates the need for MDR coverage, allowing empirical antibiotic therapy to be de-escalated. Since the main benefits of bronchoscopic quantitative cultures are decreased antibiotic selection pressure (which reduces the risk of subsequent infection with MDR pathogens) and the identification of alternative sources of infection, a clinical diagnostic approach that incorporates such principles may result in similar outcomes.

TREATMENT

TREATMENT

Ventilator-Associated Pneumonia

Many studies have demonstrated higher mortality rates with initially inappropriate empirical antibiotic therapy. The key to appropriate antibiotic management of VAP is an appreciation of the resistance patterns of the most likely pathogens in a given patient.

ANTIBIOTIC RESISTANCE

If not for the higher risk of infection with MDR pathogens (Table 121-6), VAP could be treated with the same antibiotics used for severe CAP. However, antibiotic selection pressure leads to the frequent involvement of MDR pathogens by selecting either for drug-resistant isolates of common pathogens (MRSA and Enterobacteriaceae producing extended-spectrum β-lactamases or carbapenemases) or for intrinsically resistant pathogens (*P. aeruginosa* and *Acinetobacter* species). Frequent use of β-lactam drugs, especially cephalosporins, appears to be the major risk factor for infection with MRSA and extended-spectrum β-lactamase–positive strains.

P. aeruginosa has demonstrated the ability to develop resistance to all routinely used antibiotics. Unfortunately, even if initially sensitive, *P. aeruginosa* isolates also have a propensity to develop resistance during treatment. Either de-repression of resistance genes or selection of resistant clones within the large bacterial inoculum associated with most pneumonias may be the cause. *Acinetobacter* species, *Stenotrophomonas maltophilia*, and *Burkholderia cepacia* are intrinsically resistant to many of the empirical antibiotic regimens employed (see below). VAP caused by these pathogens emerges during treatment of other infections, and resistance is always evident at initial diagnosis.

EMPIRICAL THERAPY

Recommended options for empirical therapy are listed in **Table 121-8**. Treatment should be started once diagnostic specimens have been obtained. The major factor in the selection of agents is the presence of risk factors for MDR pathogens. Choices among the various options listed depend on local patterns of resistance and—a very important factor—the patient's prior antibiotic exposure. Knowledge of the local hospital's—and even the specific ICU's—antibiogram and the local incidence of specific MDR pathogens (e.g., MRSA) is critical in selecting appropriate empirical therapy.

The majority of patients *without* risk factors for MDR infection can be treated with a single agent. Unfortunately, the proportion of patients with no MDR risk factors is <10% in some ICUs and is unknown for HAP patients. The major difference from CAP is the markedly lower incidence of atypical pathogens in VAP; the exception is *Legionella*, which can be a nosocomial pathogen, especially with breakdowns in the treatment of potable water in the hospital. The standard recommendation for patients *with* risk factors for MDR infection is for three antibiotics: two directed at *P. aeruginosa* and one at MRSA. A β-lactam agent provides the greatest coverage, yet even the broadest-spectrum agent—a carbapenem—still provides inappropriate initial therapy in up to 10–15% of cases at some centers. The emergence of carbapenem resistance at some institutions requires the addition of polymyxins to the combination-therapy options.

SPECIFIC TREATMENT

Once an etiologic diagnosis is made, broad-spectrum empirical therapy can be modified to specifically address the known pathogen. For patients with MDR risk factors, antibiotic regimens can be reduced to a single agent in most cases. Only a minority of cases require a complete course with two or three drugs. A negative tracheal-aspirate culture or growth below the threshold for quantitative cultures of samples obtained before any antibiotic change strongly suggests that antibiotics should be discontinued or that a search for an alternative diagnosis should be pursued. Identification of other confirmed or suspected sites of infection may require ongoing antibiotic therapy, but the spectrum of pathogens (and the corresponding antibiotic choices) may be different from those for VAP. A 7- or 8-day course of therapy is just as effective as a 2-week course and is associated with less frequent emergence of antibiotic-resistant strains.

The major controversy regarding specific therapy for VAP concerns the need for ongoing combination treatment of *Pseudomonas* pneumonia. No randomized controlled trials have demonstrated a benefit of combination therapy with a β-lactam and an aminoglycoside, nor have subgroup analyses in other trials found a survival benefit with such a regimen. The unacceptably high rates of clinical failure and death for VAP caused by *P. aeruginosa* despite combination therapy (see "Failure to Improve," below) indicate that better regimens are needed, perhaps including aerosolized antibiotics. Current guidelines recommend against continued combination therapy for most cases of *Pseudomonas* pneumonia.

FAILURE TO IMPROVE

Treatment failure is not uncommon in VAP, especially that caused by MDR pathogens. VAP caused by MRSA is associated with a 40% clinical failure rate when treated with standard-dose vancomycin. One proposed but unproven solution is the use of high-dose individualized treatment, although the risk of renal toxicity increases with this strategy. In addition, the MIC of vancomycin has been increasing, and a high percentage of clinical failures occur when the MIC is in the upper range of sensitivity (i.e., 1.5–2 μg/mL). Linezolid appears to be 15% more efficacious than even adjusted-dose vancomycin and is clearly preferred in patients with renal insufficiency and those infected with high-MIC isolates of MRSA. VAP due to *Pseudomonas* has a 40–50% failure rate, no matter what the regimen. Causes of clinical failure vary with the pathogen(s) and the antibiotic(s). Inappropriate initial therapy can usually be minimized by use of the recommended combination regimen (Table 121-8). However, the emergence of β-lactam resistance during therapy is an important problem, especially in infection with *Pseudomonas* and *Enterobacter* species. Recurrent VAP caused by the same pathogen is possible because the biofilm on endotracheal tubes allows reintroduction of the microorganism. Studies of VAP caused by *Pseudomonas* show that approximately half of recurrent cases are caused by a new strain.

Treatment failure is very difficult to diagnose early in the therapeutic course, and discrimination among the various potential causes is a challenge. Pneumonia due to a new superinfection, the presence of extrapulmonary infection, and drug toxicity must be considered in the differential diagnosis of treatment failure. Serial measurements of procalcitonin levels appear to track the clinical response accurately, while repeat quantitative cultures may clarify the microbiologic response.

COMPLICATIONS

Apart from death, the major complication of VAP is prolongation of mechanical ventilation, with corresponding increases in the duration of ICU stay and hospitalization. In most studies, an additional week of mechanical ventilation resulting from VAP is common. The additional expense of this complication often warrants costly and aggressive efforts at prevention.

In rare cases, necrotizing pneumonia (e.g., that due to *P. aeruginosa*) can cause significant pulmonary hemorrhage. More commonly, necrotizing infections result in the long-term complications of bronchiectasis and parenchymal scarring leading to recurrent pneumonia. Other long-term complications of pneumonia are underappreciated. Pneumonia results in a catabolic state in a patient already nutritionally at risk. The muscle loss and general debilitation from an episode of VAP often require prolonged rehabilitation and, in the elderly, often result in an inability to return to independent function and the need for nursing home placement.

FOLLOW-UP

Clinical improvement, if it occurs, is usually evident within 48–72 h of the initiation of antimicrobial treatment. Because findings on chest radiography often worsen initially during treatment, they are less helpful than clinical criteria as an indicator of clinical response in severe pneumonia.

TABLE 121-8

Empirical Antibiotic Treatment of Hospital-Acquired and Ventilator-Associated Pneumonia

NO RISK FACTORS FOR RESISTANT GRAM-NEGATIVE PATHOGEN	RISK FACTORS FOR RESISTANT GRAM-NEGATIVE PATHOGEN[a] *(CHOOSE ONE FROM EACH COLUMN)*	
Piperacillin-tazobactam (4.5 g IV q6h[b]) Cefepime (2 g IV q8h) Levofloxacin (750 mg IV q24h)	Piperacillin-tazobactam (4.5 g IV q6h[b]) Cefepime (2 g IV q8h) Ceftazidime (2 g IV q8h) Imipenem (500 mg IV q6h[b]) Meropenem (1 g IV q8h)	Amikacin (15–20 mg/kg IV q24h) Gentamicin (5–7 mg/kg IV q24h) Tobramycin (5–7 mg/kg IV q24h) Ciprofloxacin (400 mg IV q8h) Levofloxacin (750 mg IV q24h) Colistin (loading dose of 5 mg/kg IV followed by maintenance doses of 2.5 mg × [1.5 × CrCl + 30] IV q12h) Polymyxin B (2.5–3.0 mg/kg per day IV in 2 divided doses)
Risk Factors for MRSA[b] *(Add to above)*		
Linezolid (600 mg IV q12h) *or* Adjusted-dose vancomycin (trough level, 15–20 mg/dL)		

[a]Prior antibiotic therapy, prior hospitalization, local antibiogram. [b]Prior antibiotic therapy, prior hospitalization, known MRSA colonization, chronic hemodialysis, local documented MRSA pneumonia rate >10% (or local rate unknown).

Abbreviations: CrCl, creatinine clearance rate; MRSA, methicillin-resistant *Staphylococcus aureus*.

PROGNOSIS

VAP is associated with crude mortality rates as high as 50–70%, but the real issue is attributable mortality. Many patients with VAP have underlying diseases that would result in death even if VAP did not occur. Attributable mortality exceeded 25% in one matched-cohort study, while more recent studies have suggested much lower rates. Some variability in VAP mortality rates is clearly related to the type of patient and ICU studied. VAP in trauma patients is not associated with attributable mortality, possibly because many of the patients were otherwise healthy before being injured. The

causative pathogen also plays a major role. Generally, MDR pathogens are associated with significantly greater attributable mortality than non-MDR pathogens. Pneumonia caused by some pathogens (e.g., *S. maltophilia*) is simply a marker for a patient whose immune system is so compromised that death is almost inevitable.

PREVENTION

Because of the significance of endotracheal intubation as a risk factor for VAP, the most important preventive intervention is to avoid intubation or minimize its duration (Table 121-7). Successful noninvasive ventilation avoids many of the problems associated with endotracheal tubes. Strategies that minimize the duration of ventilation through daily holding of sedation and formal weaning protocols have also been highly effective in preventing VAP.

Unfortunately, a tradeoff in risks is sometimes necessary. Aggressive attempts to extubate early may result in reintubation(s) and increase aspiration, posing a risk of VAP. Heavy continuous sedation increases VAP risk, but self-extubation because of insufficient sedation is also a risk. The tradeoffs also apply to antibiotic therapy. Short-course antibiotic prophylaxis can decrease the risk of VAP in comatose patients requiring intubation, and data suggest that antibiotics decrease VAP rates overall. However, the major benefit appears to be a decrease in the incidence of early-onset VAP, which is usually caused by the less pathogenic non-MDR microorganisms. Conversely, prolonged courses of antibiotics consistently increase the risk of VAP caused by more lethal MDR pathogens. Despite its virulence and associated mortality, VAP caused by *Pseudomonas* is rare among patients who have not recently received antibiotics.

Minimizing microaspiration around the endotracheal tube cuff is also a strategy for avoidance of VAP. Simply elevating the head of the bed (at least 30° above horizontal but preferably 45°) decreases VAP rates. Specially modified endotracheal tubes that allow removal of the secretions pooled above the cuff may also prevent VAP. The risk-to-benefit ratio of transporting the patient outside the ICU for diagnostic tests or procedures should be carefully considered, since VAP rates are increased among transported patients.

The role played by overgrowth of the normal bowel flora in the stomach in the pathogenesis of VAP is questionable. MRSA and the nonfermenters *P. aeruginosa* and *Acinetobacter* species are not normally part of the bowel flora but reside primarily in the nose and on the skin, respectively. Therefore, emphasis on controlling overgrowth of the bowel flora by avoidance of agents that raise gastric pH may be relevant only in certain populations, such as liver transplant recipients and patients who have undergone other major intraabdominal procedures or who have bowel obstruction.

In outbreaks of VAP due to specific pathogens, the possibility of a breakdown in infection control measures (particularly contamination of reusable equipment) should be investigated. Even high rates of pathogens that are already common in a particular ICU may result from cross-infection. Education and reminders of the need for consistent hand washing and other infection-control practices can minimize this risk.

HOSPITAL-ACQUIRED PNEUMONIA

While significantly less well studied than VAP, HAP in non-intubated patients—both inside and outside the ICU—is similar to VAP. The main differences are the higher frequency of non-MDR pathogens and the generally better underlying host immunity in non-intubated patients. The lower frequency of MDR pathogens allows monotherapy in a larger proportion of cases of HAP than of VAP.

The only pathogens that may be more common in the non-VAP population are anaerobes. The greater risk of macroaspiration by non-intubated patients and the lower oxygen tensions in the lower respiratory tract of these patients increase the likelihood of a role for anaerobes. While more common in patients with HAP, anaerobes usually contribute only to polymicrobial pneumonias. As in the management of CAP, specific therapy targeting anaerobes probably is not needed since many of the recommended antibiotics are active against anaerobes.

Diagnosis is even more difficult for HAP in the non-intubated patient than for VAP. Lower respiratory tract samples appropriate for culture are considerably more difficult to obtain from non-intubated patients. Many of the underlying diseases that predispose a patient to HAP are also associated with an inability to cough adequately. Since blood cultures are infrequently positive (<15% of cases), the majority of patients with HAP do not have culture data on which antibiotic modifications can be based. Therefore, de-escalation of therapy is less likely in patients with risk factors for MDR pathogens. Despite these difficulties, the better host defenses in non-ICU patients result in lower mortality rates than are documented for VAP. In addition, the risk of antibiotic failure is lower in HAP.

GLOBAL IMPACT

From the available data, it is virtually impossible to accurately assess the impact of pneumonia from a global perspective. Any differences in incidence, disease burden, and costs across different age, ethnic, and racial groups are compounded by differences among countries in terms of etiologic pathogens, resistance rates, access to health-care and diagnostic facilities, and vaccine availability and usage.

A standard approach with clearly defined outcome measures is needed before the impact of pneumonia can be accurately evaluated. However, simple extrapolation from U.S. data for CAP and HAP/VAP shows that pneumonia has a significant impact on quality of life, morbidity, health costs, and mortality rates and that this impact has implications for patients and for society as a whole.

FURTHER READING

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