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# 38 How Does One Diagnose and Manage Severe Community-Acquired Pneumonia?

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Community-acquired pneumonia (CAP) is the major cause of infection-related death in developed countries and also is a common etiology of systemic sepsis and critical illness. The mortality rate in severe community-acquired pneumonia (SCAP) is about 30%. This is far higher than the mortality observed from pneumonia managed outside of the hospital or in the hospital but outside of the intensive care unit (ICU). Therefore, to ensure proper management and therapy, it is imperative to recognize this illness as soon as possible. Delays in recognizing severe forms of CAP can increase mortality. Indeed, a number of studies show that delayed management in the ICU is associated with a higher risk for death than when the disease is managed expectantly in the ICU, at the first signs of severe illness.[1]

There is no uniformly useful or accepted definition of SCAP, nor are there standard criteria for admission to the ICU. Current Infectious Diseases Society of America and American Thoracic Society (IDSA/ATS) guidelines define SCAP using major criteria such as respiratory failure (need for assisted ventilation) or septic shock requiring vasopressors.[2] Three additional minor criteria are used to diagnose SCAP: respiratory rate 30 breaths/minute or higher, $Pa_{O_2}/F_{IO_2}$ ratio 250 or less, multilobar infiltrates, confusion or disorientation, blood urea nitrogen (BUN) 20 mg/dL or higher, leukopenia (white blood cell count $< 4000$ cells/$mm^3$), thrombocytopenia ($<100{,}000$ platelets/$mm^3$), hypothermia (temperature $< 36°C$), and hypotension requiring aggressive fluid resuscitation. Other possible minor criteria that should affect the decision to admit the patient to the ICU include hypoglycemia (in nondiabetic patients), alcohol withdrawal, hyponatremia, unexplained metabolic acidosis or lactic acidosis, and asplenia.

Although there have been attempts to develop objective criteria for SCAP, most case series have defined this entity simply as CAP requiring admission to the ICU. In one study of a national database in the United Kingdom,[1] CAP accounted for 5.9% of all ICU admissions. Early admission appeared to be preferable in the setting of severe illness because the mortality rate was 46.3% in those admitted to the ICU within 2 days of hospital admission but rose to 50.4% in those admitted at 2 to 7 days and to 57.6% in those admitted more than 7 days after hospital admission. Other studies have shown improved outcomes in SCAP when initial therapy is appropriate. A 5-year retrospective French study[3] used multivariate analysis to demonstrate that the effectiveness of the initial therapy appeared to be the most significant prognostic factor. In fact, this was the only prognostic factor that constituted a modifiable medical intervention.

## WHO GETS SEVERE COMMUNITY-ACQUIRED PNEUMONIA?

### Risk Factors for Severe Forms of Community-Acquired Pneumonia

About 45% to 65% of patients with SCAP have coexisting illnesses. Conversely, patients who are chronically ill have an increased likelihood of developing a complicated pneumonic illness[4] (Table 38-1). The most common chronic illnesses in these patients are respiratory disease such as chronic obstructive lung disease (COPD), cardiovascular disease, and diabetes mellitus. In addition, certain habits, such as cigarette smoking and alcohol abuse, also are common in those with SCAP. Indeed, cigarette smoking has been identified as a risk factor for bacteremic pneumococcal infection.[5] Other common illnesses in those with CAP include malignancy and neurologic disorders (including seizures). Milder forms of pneumonia may be more severe on presentation if patients have not received antibiotic therapy before hospital admission. In addition, the ability to contain the infectious challenge, which may be related to genetic differences in the immune response, may predispose certain individuals to more severe forms of infection and adverse outcomes. This may be reflected in a family history of severe pneumonia or adverse outcomes from infection.[6–14] It appears likely that SCAP results when inflammation is either insufficient to contain the infection or so exuberant that the host response affects the uninvolved lung (leading to acute respiratory distress syndrome) or the systemic circulation (leading to severe sepsis).[8]

## PREDICTORS OF OUTCOME

The most commonly used predictors of outcome from pneumonia are two scoring systems, the Pneumonia Severity Index (PSI)[15] and the British Thoracic Society rule.[16]

**Table 38-1 Risk Factors for Developing Severe Community-Acquired Pneumonia**

- Advanced age (>65 yr)
- Comorbid illness: especially if decompensated
  - Chronic respiratory illness (including chronic obstructive pulmonary disease), cardiovascular disease, diabetes mellitus, neurologic illness, renal insufficiency, malignancy
- Cigarette smoking (risk for pneumococcal bacteremia)
- Alcohol abuse
- Absence of antibiotic therapy before hospitalization, or inappropriate therapy
- Residence in a chronic care facility
- Poor functional status
- Failure to contain infection to its initial site of entry
- Immune suppression (corticosteroids, other illnesses)
- Genetic polymorphisms in the immune response

The latter rule recently has been modified to the CURB-65 score. This is an acronym for the following: *c*onfusion, serum *u*rea nitrogen level higher than 19.6 mg/dL, *r*espiratory rate 30 breaths/minute or higher, low systolic (≤90 mm Hg) or diastolic (≤60 mm Hg) *b*lood pressure, and age older than *65* years. These two scoring systems are valid in identifying patients at low risk for mortality. Each, however, has limitations. These limitations are most apparent when the systems are used to identify those with SCAP. Ideally, the two complement one another.[17] The PSI heavily weights age and comorbidity but does not necessarily measure the severity of acute illness, relying on vital sign abnormalities that fall either above or below a dichotomous variable threshold. Thus, it may overestimate severity of illness in older patients and underestimate severity in younger individuals without comorbid illness. Conversely, the CURB-65 criteria may not adequately consider the presence of comorbid illness, particularly those in which pneumonia has induced decompensation.

Several studies have compared both prognostic tools in the same population.[16,18–22] In one recent study, both the PSI and the CURB-65 were good at predicting mortality and identifying low-risk patients. However, the CURB-65 appeared to be more discriminating in defining mortality risk in the severely ill.[20] Another study by España and colleagues used both the PSI and the CURB-65 to evaluate a large number of inpatients and outpatients with CAP.[21] In this investigation, the CURB-65 (and its simpler CRB-65 version, which excludes measurement of BUN and thus can be used in outpatients) accurately predicted 30-day mortality, the need for mechanical ventilation, and perhaps the need for hospitalization. In addition, the CURB-65 criteria correlated with the time to clinical stability. Thus, a higher score predicted a longer duration of intravenous therapy and a longer length of hospital stay. The PSI predicted mortality. However, as demonstrated in other studies, the PSI was not good at predicting the need for ICU admission. España and colleagues found that the CURB-65 also could not predict the need for ICU admission reliably. However, other investigators found the CURB-65, although still limited, to be more accurate than the PSI for predicting need for ICU admission.[19]

In a study done in a tertiary care hospital in Spain,[22] most patients with the highest possible PSI category (risk class V) were treated on a medical ward, with only 20% treated in the ICU. The investigators found that when patients were admitted to the ICU, they tended to get more of their PSI points from acute rather than chronic illness. The reverse was true for those PSI class V patients who were not admitted to the ICU. Data from patients with CAP admitted to two tertiary hospitals in Texas[23] analyzed retrospectively demonstrated that, although the patients in the ICU had a higher PSI score than the ward patients, the ICU patient cohort (145 patients) included patients in all PSI classes, with 30% falling into low-risk PSI groups (classes I to III). These findings are similar to data reported by Ewig and associates,[19] indicating that the PSI was good for predicting CAP mortality but not for determining the need for ICU care. Prognostic tools used to identify the need for intensive care or to predict mortality are summarized in Table 38-2.[16,18–21,24–30]

Recently, España and colleagues tried to develop a more specific rule for ICU admission. They examined records from 1057 patients and determined that the need for ICU admission was defined by the presence of one of two major criteria: arterial pH less than 7.30 or systolic blood pressure less than 90 mm Hg.[21] In the absence of these criteria, SCAP also could be identified by the presence of two of six minor criteria. These included confusion, BUN greater than 30 mg/dL, respiratory rate greater than 30 breaths/minute, $Pa_{O_2}/F_{IO_2}$ ratio less than 250, multilobar infiltrates, and age at least 80 years. When these criteria were met, the tool was 92% sensitive for identifying those with SCAP and was more accurate than the PSI or CURB-65 criteria, although not quite as specific as the CURB-65 rule.[21]

A number of recent investigations have examined biomarkers in serum to measure CAP severity and to predict the outcome. These studies have focused on C-reactive protein (CRP), procalcitonin (PCT), and cortisol.[31–36]

In a study of 185 patients (144 inpatients and 44 outpatients) who had PCT measured within 24 hours of the diagnosis, CAP levels correlated with PSI score (higher in classes III to V than in I and II) and the development of complications (higher with empyema, mechanical ventilation, and septic shock). Levels also were increased in those who died compared with those who did not.[33] Serial measurements of PCT also have been used to define prognosis in SCAP patients. Investigators have reported that nonsurvivors have a significantly higher PCT level than survivors on day 1. With serial measurements, survivors had a decrease in PCT levels, whereas nonsurvivors had an increase by day 3.[35]

In a recent study of 278 patients presenting to an emergency department in Switzerland with pneumonia,[36] cortisol levels also could be used to predict severity of illness and outcome (death). Free and total cortisol levels correlated with severity of illness, as reflected by PSI score, with a level of total cortisol above 960 nmol/L having a sensitivity of 75% and a specificity of 71.7% for predicting mortality. These data should be viewed cautiously because some recent studies have questioned the reliability of serum cortisol levels in patients with acute septic illness.

## Table 38-2 Comparison of Studies for Prognostic Scores on Pneumonia Severity

| Study | No. of Patients | Outcome Predictor | Prediction Rule | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|
| Farr B, 1991[24] | 245 | Mortality | Original BTS rule 1 | 70 | 84 | 29 | 97 |
| Karalus N, 1991[25] | 92 | Mortality | Original BTS rule 1 | 83 | 80 | 23 | 99 |
| Ewig, 1995[26] | 92 | Mortality | Original BTS rule 1 | 65 | 73 | 21 | 95 |
| | | | Original BTS rule 2 | 47 | 88 | 31 | 94 |
| Neill A, 1996[27] | 122 deceased* | Mortality | Modified BTS (CURB $\geq$ 2)† | 95 | 71 | 22 | 99 |
| | | | Original BTS rule 1 | 90 | 76 | 25 | 99 |
| | | | Original BTS rule 2 | 90 | 88 | 33 | 97 |
| Ewig S, 1998[28] | 395 | Need for ICU admission | Modified ATS | 78 | 94 | 75 | 95 |
| Conte H, 1999[29] | 2356 | Mortality | Original BTS rule 1‡ | 50 | 70 | NR | NR |
| Lim W, 2000[18] | 181 deceased* | Mortality | Modified BTS (CURB $\geq$ 2) | 66 | 73 | NR | NR |
| Lim W, 2003[16] | 1068 | 30-day mortality | Modified BTS (CURB-65 $\geq$ 3) | 68.1 | 74.9 | 22.4 | 95.7 |
| | | | Derivation cohort (718 pts)† | 75 | 74.7 | 23.4 | 96.7 |
| | | | Validation cohort (214 pts) | | | | |
| Ewig, 2004[19] | 696 | 30-day mortality | Modified ATS | 94 (95% CI, 82.5-98.7) | 93 (95% CI, 90.6-94.7) | 49 (95% CI, 38.2-59.7) | 99.5 (95% CI, 98.5-99.9) |
| | | | Modified BTS (CURB $\geq$ 2) | 51 (95% CI, 35.5-67.1) | 80 (95% CI, 76.3-83.1) | 16 (95% CI, 10.1-23.3) | 96 (95% CI, 93.4-97.3) |
| Aujesky D, 2005[20] | 3181 | Mortality | PSI $\geq$ 4 | 79 (95% CI, 71-85) | 70 (95% CI, 68-72) | 13 (95% CI, 11-17) | 99 (95% CI, 98-99) |
| | | | CURB $\geq$ 2 | 47 (95% CI, 39-55) | 85 (95% CI, 84-87) | 13 (95% CI, 11-17) | 97 (95% CI, 96-98) |
| | | | CURB-65 $\geq$ 3 | 45 (95% CI, 37-53) | 87 (95% CI, 86-88) | 14 (95% CI, 11-18) | 97 (95% CI, 96-98) |
| España, 2006 | 1057 | Mortality, need for mechanical ventilation and/or septic shock | SCAP prediction rule†§ | 92.1 | 95.97 | 21.4 | 99.2 |
| | | | Modified ATS | 51.3 | 95.9 | 49.4 | 96.2 |
| | | | CURB-65 $\geq$ 3 | 68.4 | 86.8 | 28.6 | 97.3 |
| | | | PSI $\geq$ 4 | 94.7 | 68.1 | 18.7 | 99.4 |
| | | | Adjusted PSI (classes I-III with oxygen desaturation and PSI $\geq$ IV) | 97.4 | 57.5 | 15.1 | 99.7 |

*Indicates derivation studies.
†Case-control studies.
‡All patients $\geq$ 65 yr or older.
§9/20 Variables also present in PSI + multi-lobar chest radiograph.
ATS, American Thoracic Society; BTS, British Thoracic Society; CI, confidence interval; CURB, confusion, serum urea, respiratory rate, blood pressure; ICU, intensive care unit; NPV, negative predictive value; NR, not reported; PPV, positive predictive value; PSI, Pneumonia Severity Index; SCAP, severe community-acquired pneumonia.

## DIAGNOSTIC TESTING

### History and Physical Examination

History should focus on the presence of symptoms suggesting respiratory infection (fever, cough, purulent sputum, pleuritic chest pain, dyspnea) along with information suggesting serious illness. The history should thus focus on the presence of comorbid illness, recent hospitalization, and recent antibiotic therapy. In addition, there are certain clinical conditions associated with specific pathogens in patients with CAP, and these associations should be evaluated when obtaining a history (Table 38-3).[2] For example, if the presentation is subacute, following contact with birds, rats, or rabbits, 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* is a concern with rabbit exposure; hantavirus with exposure to mice droppings in endemic areas; *Chlamydia psittaci* with exposure to turkeys or infected birds; and *Legionella* species with exposure to contaminated water sources (saunas). After influenza superinfection with pneumococcus, *Staphylococcus aureus* (including methicillin-resistant *S. aureus* [MRSA]) and *Haemophilus influenzae* should be considered. With travel to endemic areas in Asia, the onset of respiratory failure after a viral illness should lead to suspicion of a viral pneumonia, which could be severe acute respiratory syndrome (SARS) or avian influenza. Endemic fungi (coccidioidomycosis, histoplasmosis, and blastomycosis) occur in well-defined geographic areas and may present acutely with symptoms that overlap with acute bacterial pneumonia.

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 *Mycoplasma pneumoniae* or *Chlamydophila pneumoniae* that can lead to such complications as bullous myringitis, skin rash, pericarditis, hepatitis, hemolytic anemia, or meningoencephalitis. An attentive physical examination may help identify patients with severe pneumonia. One study[37] showed that in elderly patients, elevation of the respiratory rate can be the initial presenting sign of pneumonia, preceding other clinical findings by as much as 1 to 2 days. Indeed, tachypnea is present in more than 60% of all patients, being found more often in elderly than in younger patients with pneumonia. In addition, the counting of respiratory rate can identify the patient with severe illness, who commonly have a rate higher than 30 breaths/minute.

### Recommended Diagnostic Testing

In addition to a constellation of suggestive clinical features, a diagnosis of CAP can only be made with the finding of a

Table 38-3 **Epidemiologic Conditions Related to Specific Pathogens in Patients with Community-Acquired Pneumonia**

| Condition | Commonly Encountered Pathogens |
|---|---|
| Alcoholism | *Streptococcus pneumoniae* (including drug-resistant *S. pneumoniae*), anaerobes, gram-negative bacilli, tuberculosis |
| Chronic obstructive pulmonary disease; smoker | *S. pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Legionella* species |
| Nursing home residency | *S. pneumoniae*, gram-negative bacilli, *H. influenzae*, *Staphylococcus aureus*, anaerobes, *Chlamydia pneumoniae*, tuberculosis |
| Poor dental hygiene | Anaerobes |
| Epidemic legionnaires disease | *Legionella* species |
| Exposure to bats | *Histoplasma capsulatum* |
| Exposure to birds | *Chlamydia psittaci*, *Cryptococcus neoformans*, *H. capsulatum* |
| Exposure to rabbits | *Francisella tularensis* |
| Travel to southwest United States | Coccidioidomycosis |
| Exposure to farm animals or parturient cats | *Coxiella burnetii* (Q fever) |
| Influenza active in community | Influenza, *S. pneumoniae*, *S. aureus*, *H. influenzae* |
| Suspected large-volume aspiration | Anaerobes, chemical pneumonitis, obstruction |
| Structural disease of lung (e.g., bronchiectasis, cystic fibrosis) | *Pseudomonas aeruginosa*, *Pseudomonas cepacia*, *S. aureus* |
| Injection drug use | *S. aureus*, anaerobes, tuberculosis, *Pneumocystis carinii* |
| Endobronchial obstruction | Anaerobes |
| Recent antibiotic therapy | Drug-resistant pneumococci, *P. aeruginosa* |

new radiographic lung infiltrate. These findings are not specific for pneumonia and generally cannot help define an etiologic pathogen. Thus, microbiologic data are needed.[4] Although chest radiographic patterns generally are not useful for identifying the etiology of CAP, certain findings such as pleural effusion (pneumococcus, *H. influenzae*, *M. pneumoniae*, pyogenic streptococci) and cavitation (*Pseudomonas aeruginosa*, *S. aureus*, anaerobes, MRSA, tuberculosis) can suggest certain groups of organisms. It often is difficult to define the etiologic pathogens in patients with CAP because up to half of such patients have no identified etiology even with extensive diagnostic testing that includes cultures of blood and sputum. Although there is controversy about the value of diagnostic testing in patients with CAP, extensive routine testing is recommended for those admitted to the ICU.[2] Several studies have shown that establishing an etiologic diagnosis does not improve the outcome of SCAP and that outcome is only improved if empirical and broad-spectrum early therapy is given, targeting the likely etiologic pathogens. However, diagnostic testing may have value for the purpose of narrowing and focusing therapy and for guiding management in the patient who is not responding to empirical therapy.[38]

When collecting samples for diagnostic testing, it is important to start empirical antibiotics because delays in therapy have been associated with increased mortality. In addition to a chest radiograph, all SCAP patients should have blood and lower respiratory tract (sputum, endotracheal aspirate, bronchoalveolar lavage, or bronchoscopic specimen) cultures, arterial blood gas analysis,[39] 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. The yield of a positive culture of pleural fluid is low, but the information acquired when the cultures are positive have a substantial effect on the management, not only for antibiotic choice, but also for the indications for drainage.[2] Patients with SCAP should have two sets of blood cultures,[2,4,40] 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 liver disease, hypotension, fever or hypothermia, tachycardia (pulse > 125 beats/minute), elevated BUN, serum sodium level less than 130 mEq/L, and white cell count lower than 5000 cells/μL or higher than 20,000 cells/μL.[40] The presence of bacteremia may not worsen prognosis but does allow identification of drug-resistant organisms, although most positive blood cultures in CAP reveal pneumococcus.[4]

Sputum culture should be accompanied by 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 empirical therapy by enhancing the suspicion for organisms that are not covered by routine empirical therapy (such as *S. aureus*, suggested by 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* species infection can be made by urinary antigen testing because this is the test most likely to be positive at the time of admission. One shortcoming is that this test is specific only for serogroup I infection.[2] Examination of concentrated urine for pneumococcal antigen also may be valuable. In cases in which viral etiology is suspected, influenza direct fluorescent antibody testing can be performed, and the result is usually available in few hours. For other respiratory viruses, testing might be of use, particularly in the setting of outbreaks.[4] Bronchoscopy is not indicated as a routine diagnostic test but may be needed in some patients with severe forms of CAP to establish an etiologic diagnosis in order to focus the initially broad-spectrum empirical therapy to a simpler regimen.[2]

## BACTERIOLOGY

### Identifying Patients with Health Care–Associated Pneumonia

Some patients with severe pneumonia are admitted to the hospital after outpatient contact with the health care environment and thus do not have traditional CAP; rather, the diagnosis is health care–associated pneumonia (HCAP). These patients are admitted from a nursing home or extended care facility, have been in the hospital sometime during the past 90 days, have undergone hemodialysis, or are receiving ongoing wound care. Because of contact with the hospital environment, these patients are at risk for infection with multidrug-resistant (MDR) gram-negative pathogens and MRSA. Thus, they need a different approach to therapy.[41,42] In the 2005 IDSA/ATS Nosocomial Pneumonia guidelines, HCAP was considered a form of nosocomial infection,[43] and Medicare has exempted such patients from therapy that is compliant with CAP "core measures." We have chosen to include HCAP in the discussion of CAP because these are the patients who develop severe illness and are at risk for infection with enteric gram-negative bacteria and MRSA. However, patients admitted from a nursing home still may have infections caused by atypical pathogens and *Legionella* species.[44,45] Some patients with HCAP have pathogens similar to SCAP, whereas others have pathogens similar to severe nosocomial pneumonia. Therapy varies accordingly. Some examples of HCAP patients at high risk for MDR pathogens are those with prior antibiotics exposure (within the past 3 to 6 months), those with poor functional status, and those with recent hospitalization.[46–48]

### Common Pathogens

The most common cause of SCAP is pneumococcus (*Streptococcus pneumoniae*).[4] This organism accounts for two thirds of bacteremic pneumonia and are the most frequent cause of lethal CAP.[2,49] At least 40% of cases are resistant to penicillin or other antibiotics, leading to the term *drug-resistant S. pneumoniae* (DRSP). Currently, most penicillin resistance in the United States is of the "intermediate" type (penicillin minimum inhibitory concentration, or MIC, of 0.1 to 1.0 mg/L) rather than the high-level type (penicillin MIC of 2.0 or more).[50] Pneumococcal resistance to other antibiotics, including macrolides and trimethoprim-sulfamethoxazole, also is common, but the clinical relevance

and effect on outcome of these in vitro findings are uncertain. One study, corroborated by the opinion of many experts, found that only organisms with a penicillin MIC higher than 4 mg/L were associated with an increased risk for death.[51] In a prospective international study of 844 patients with pneumococcal bacteremia,[52] in vitro resistance to β-lactams was associated with little in the way of clinical impact. Discordant therapy with penicillins, cefotaxime, and ceftriaxone did not result in a higher mortality. However, discordant therapy with cefuroxime led to a worse clinical outcome than if the organism were sensitive to this agent. Although DRSP is common, quinolone resistance is unusual. Doern and associates[50] observed that, although penicillin resistance was present in 34.2% of pneumococci, quinolone resistance was rare. However, 21% of organisms had a single first-step mutation (par C) that did not confer resistance but could predispose to clinical resistance in the presence of a second mutation (gyr A). This situation mandates close observation.

All patients with SCAP should be considered at risk for DRSP. In addition, those admitted to the ICU can have infection with atypical pathogens that can account for up to 20% of infections, either as primary infection or as copathogens. The identity of these organisms varies with time and geography. In some areas, *Legionella* species is a common cause of SCAP, whereas in others, *C. pneumoniae* or *M. pneumoniae* infection predominates.[4] Other important causes of SCAP include *H. influenzae*, *S. aureus*, MRSA (especially after influenza), and enteric gram-negative bacteria (including *P. aeruginosa*). Risk factors for gram-negative bacteria include underlying COPD (especially with corticosteroid therapy), recent hospitalization, prior antibiotics, bronchiectasis, and the presence of HCAP.[47] The specific risks for *P. aeruginosa* include the presence of structural lung disease (bronchiectasis), COPD, treatment with broad-spectrum antibiotics within 7 days of presentation, chronic steroid use, malignancy, and malnutrition.[2,47] Rapid radiographic spread of the disease is also a clue to the presence of *P. aeruginosa* infection. In a multicenter Spanish study of 529 patients with SCAP, 15 of 20 patients (75%) with *P. aeruginosa* had rapidly progressive illness because antimicrobial treatment at admission was inadequate.[53]

Recently, a toxin-producing strain of MRSA has been described in patients with CAP after influenza and other viral infections. This community-acquired MRSA is biologically and genetically distinct from the MRSA that causes nosocomial pneumonia. It is more virulent and necrotizing and is associated with the production of the Panton-Valentine leukocidin (PVL).[54,55] Viruses can be a cause of SCAP. Culprits include influenza virus as well as parainfluenza virus and epidemic viruses such as coronavirus (which causes SARS) and avian influenza.[2,56] 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 in patients who have epidemiologic risk factors for specific pathogens, as discussed previously. In addition, the presence of certain "modifying factors" increases the likelihood of CAP caused by DRSP and gram-negative bacteria.[47,57] 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.[57,58] The risk factors for gram-negative bacteria were mentioned previously and include the presence of HCAP. In addition, aspiration is more commonly associated with gram-negative pneumonia than with anaerobic infection in the institutionalized elderly population.[59]

## TREATMENT

For ICU-admitted CAP, initial therapy should be directed at DRSP, *Legionella* species, and other atypical pathogens, enteric gram-negative bacteria (including *P. aeruginosa*), and other selected organisms. Drug selection should be based on appropriate historical and epidemiologic data. Therapy is stratified depending on whether the patient is at risk for *P. aeruginosa* (based on the risk factors listed previously). In all treatment algorithms, no ICU-admitted CAP patient should receive empirical monotherapy, even with one of the new quinolones.[57] This recommendation is based on the fact that the efficacy (especially for meningitis complicating pneumonia), effective dosing, and safety of any single agent, including quinolone monotherapy, has not been established for ICU-admitted CAP patients. In one recent study comparing high-dose levofloxacin to a β-lactam–quinolone combination, the single-agent regimen was overall effective. However, patients in septic shock were excluded, and there was a trend to a worse outcome with monotherapy for individuals treated with mechanical ventilation.[60] In another study of SCAP, the use of a β-lactam–macrolide combination had a survival advantage compared with quinolone monotherapy.[61]

If the patient has no pseudomonal risk factors, therapy should be limited to a selected intravenous β-lactam (cefotaxime, ceftriaxone, ertapenem, or 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 antipseudomonal quinolone) or levofloxacin (750 mg daily). Alternatively, a three-drug regimen involving an antipseudomonal β-lactam plus an aminoglycoside plus either an intravenous and antipneumococcal quinolone (levofloxacin or moxifloxacin) or a macrolide[2,57,62] can be used. One of the justifications for being familiar with these recommendations is the finding that if patients are treated with these types of regimens, outcomes are improved.[53,63] Several studies have shown that guideline compliance can improve outcome and that nonadherence can lead to a delay in clinical resolution.[63–67]

All these regimens have alternatives, and it is not clear whether one regimen is better than another. However, in the selection of an empirical therapy regimen, it is necessary to know what antibiotic the patient has received within the past 3 months and to choose an agent that is in a different class. Indeed, repeated use of the same class

of antibiotic may drive resistance to that class, especially if the pathogen is pneumococcus. In one study, use of a penicillin, cephalosporin, trimethoprim-sulfa, or levofloxacin in the 3 months preceding pneumococcal bacteremia led to an increased likelihood that the bacteremic pathogen would be resistant to the recently used therapeutic agent.[68]

In addition to choosing antibiotic therapy, as discussed previously, it is important to give the first dose of antibiotic as soon as possible after the diagnosis is established. For all patients with CAP, timely administration of antibiotics reduces mortality. This is especially true if the first dose is given within 4 to 6 hours, but even more rapid administration is necessary for those with severe illness. For example, in patients with sepsis, each hour of delay in the start of antibiotic therapy increases mortality by 7.6%.[69]

The antibiotic regimens discussed previously all cover for atypical pathogens using either a macrolide or a quinolone. Data indicate that such an approach reduces mortality, especially in those with severe illness.[70–72] Even in patients with pneumococcal bacteremia, the use of combination therapy (generally with the addition of a typical pathogen coverage to pneumococcal coverage) has been associated with reduced mortality relative to monotherapy.[72] In one study, the benefit of adding a second agent applied to those pneumococcal bacteremia patients who were critically ill but not to other populations.[73] Rodriguez and colleagues found a benefit to adding a second agent for all patients with SCAP and shock.[74] This benefit applied if the agent added was either a macrolide or a quinolone.

Certain adjunctive therapies should be considered, although the recommendations on these strategies have less supportive evidence. These include oxygen, chest physiotherapy (in those with at least 30 mL of sputum daily and a poor cough response), aerosolized bronchodilators, and corticosteroids (if hypotension and possible relative adrenal insufficiency is suspected).[75–77] 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 CAP patients with an Acute Physiology and Chronic Health Evaluation (APACHE) II score higher than 25, a PSI class of IV or V, and a CURB-65 score of at least 2. There was also benefit in those with pneumococcal infection and with inadequate therapy, although the benefit was minimal in those treated with adequate therapy.[75]

Corticosteroids may be helpful in SCAP because of their immunomodulating effect. One randomized controlled trial of 48 patients comparing hydrocortisone infusion (240 mg/day) to placebo found that steroid therapy reduced mortality, length of stay, and duration of mechanical ventilation.[76] Another recent study involved a retrospective analysis of 308 patients with SCAP (based on PSI score), some of whom had received systemic corticosteroids for reasons other than pneumonia while being treated for CAP.[77] Therapy with systemic corticosteroids was found to be independently associated with decreased mortality. Large randomized controlled studies are needed to make recommendations on the routine use of corticosteroids in SCAP, but the data suggest that steroid use is not dangerous if this therapy is needed for other reasons in patients with SCAP.[78]

There are few data on the proper duration of therapy in patients with CAP, especially in those with severe illness. Even in the presence of pneumococcal bacteremia, short durations of therapy may be possible. It also may be possible to rapidly 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 empirical therapy at the correct dose. The presence of extrapulmonary infection (e.g., meningitis and empyema) and the identification of certain pathogens (e.g., bacteremic *S. aureus* and *P. aeruginosa)* may suggest a need for a longer durations of therapy. Treatment of *Legionella pneumophila* pneumonia may require 14 or more days of therapy. Recent data, however, suggest that quinolone therapy may the best approach to management and that treatment for as little as 5 days with levofloxacin, 750 mg, may be effective.[79] The switch to oral therapy, even in severely ill patients, may be facilitated by the use of quinolones because these agents are highly bioavailable and achieve the same serum levels with oral therapy as with intravenous therapy.

There is controversy about the need for empirical therapy directed against community-acquired MRSA. Most experts recommend that this organism be targeted with empirical therapy only 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 that reason, it may be necessary to add clindamycin to vancomycin or to use linezolid (with rifampin in severe illness) because both these latter agents can inhibit toxin production.[55]

## Nonresponding Pneumonia

Overall, 6% to 15% of patients hospitalized with CAP do not respond to initial therapy.[4] Mortality is increased for these nonresponders.[80] In patients admitted to the ICU, the risk for failure to respond is high, and as many as 40% of the patients experience deterioration even after initial stabilization in the ICU.[81] Because pneumonia is a clinical syndrome, not all patients with this diagnosis actually have lung infection. Indeed, 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 these situations may lead to an apparent nonresponse to therapy.

Nonresponding patients should be evaluated for alternative diagnoses (inflammatory lung disease, atelectasis, heart failure, malignancy, pulmonary hemorrhage, pulmonary embolus, nonpneumonic infection), a resistant or unusual pathogen (including tuberculosis and fungal infection), pneumonia complication (empyema, lung abscess, drug fever, antibiotic-induced colitis), or a secondary site of infection (central line infection, intra-abdominal infection) (Table 38-4). The search for a specific etiologic agent has been evaluated. In one study, a change in the antibiotic regimen based on microbiologic studies,

**Table 38-4 Factors Present in Patients with Nonresponding Pneumonia**

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| **NONINFECTIOUS DIAGNOSIS** |
| • Inflammatory lung disease: bronchiolitis obliterans, pulmonary fibrosis<br>• Atelectasis<br>• Heart failure<br>• Respiratory malignancy<br>• Pulmonary hemorrhage: Goodpasture syndrome, granulomatous vasculitis, systemic lupus erythematosus<br>• Pulmonary emboli with infarction |
| **PATHOGEN RELATED** |
| • Resistant bacteria<br>• Unusual pathogen (unsuspected): fungus, *Mycobacterium tuberculosis* |
| **COMPLICATIONS OF PNEUMONIC PROCESS** |
| • Empyema<br>• Lung abscess<br>• Metastatic infection: bacterial endocarditis, intra-abdominal infection |
| **COMPLICATIONS OF TREATMENT WITH INTRAVENOUS ANTIBIOTICS** |
| • Drug-induced fever<br>• Central line infection<br>• Antibiotic-induced colitis |

as opposed to empirical changes, did not alter the mortality in nonresponders.[82]

Although most patients respond to therapy rapidly,[83] those with severe pneumonia tend to have a more protracted course.[84] The evaluation of a nonresponding patient should be individualized but may include computed tomography of the chest, pulmonary angiography, bronchoscopy, and occasionally open-lung biopsy. Bronchoscopy may be valuable in immunocompromised and immunosuppressed patients to help identify the presence of *Pneumocystis* species, viruses, fungi, and mycobacterial infection.

## AUTHORS' RECOMMENDATIONS

- Recognition of SCAP at the earliest possible time point improves outcome.
- There is no uniformly accepted definition of SCAP, and prognostic scoring systems such as the PSI and CURB-65 are decision support tools only.
- Diagnostic testing for SCAP should focus on historical data increasing the risk for infection with specific pathogens and on obtaining a chest radiograph, blood cultures, sputum culture, and urinary antigen testing for *Legionella* and *Pneumococcus* species.
- All patients with SCAP need therapy for drug-resistant pneumococcus and atypical pathogens (including *Legionella* species), and consideration of risk factors for enteric gram-negative bacteria, including *P. aeruginosa*. Some patients, especially those diagnosed with influenza, are at risk for MRSA. Patients who come from nursing homes have HCAP and may be at risk for drug-resistant organisms.
- All patients with SCAP require combination therapy that is based on whether the patient is at risk for *P. aeruginosa*. No patient should receive empirical monotherapy.
- Adjunctive therapy for SCAP includes chest physiotherapy and consideration of corticosteroids (as immune modulators) and activated protein C.

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