Community-acquired pneumonia (CAP) is a serious condition that could lead to poor outcomes, including death, longer hospital stay, and high health care cost. The sickest patients who have CAP are those who require hospitalization and are usually admitted to the ICU. CAP and influenza are the first leading causes of death from infectious diseases in the United States.\(^1,2\) CAP represents one of the most common causes of ICU admission.\(^3\) The term “severe CAP” identifies a group of patients who have severe disease, who are prone to have complications and poor outcomes, and who require a higher level of care. It is clear that the patients who require ICU admission differentiate from the less severe patients who have CAP in various ways. There is some controversy related to the term “severe,” however, because it does not differentiate well if this is severe enough to be admitted to the hospital, severe enough to...
require ICU admission, or severe enough because of the signs and symptoms that trigger a higher level of care despite the location in the hospital setting. The definition used in this article includes studies and information of patients severely ill with CAP who require ICU admission, have a higher risk for dying because of the condition, and require interventions that could only be provided in a higher-acuity level of care. The article reviews the most recent and relevant data regarding the epidemiology, microbiology, severity of the disease, therapeutic strategies, and preventive measures of severe CAP.

EPIDEMIOLOGY

CAP occurs in approximately 4 million adults in the United States and it accounts for 10,000,000 physician visits, 500,000 hospitalizations, and 45,000 deaths each year. CAP mortality is variable depending on the site of care; it is less than 1% in the outpatient setting, around 5% in inpatients not requiring ICU care, up to 25% in intubated patients, and near 50% in ICU patients requiring vasopressors. Up to 36% of patients who have CAP require admission to the ICU and despite advances in antimicrobial therapy and supportive measures the mortality in this group of patients ranges from 21% to 58%. The main causes of death in patients who have severe CAP include refractory hypoxemia, refractory shock, and other pneumonia-related complications, predominantly multiorgan failure. In addition, patients who have severe CAP tend to stay longer in the hospital, which is associated with higher hospital cost. It is estimated that patients in the ICU compared with ward patients carry higher cost driven by the longer length of stay: 23 days and $21,144 for ICU patients versus 6 days at a cost of approximately $7500 for ward patients.

The recognition of patients at risk for severe CAP who may require ICU admission is critical. The most important risk factors associated with the need for hospitalization and particularly for admission to the ICU are patients who have CAP with prior comorbid conditions or received prior antibiotic therapy. Recent prior intravenous antibiotic therapy has been associated with multidrug-resistant pathogens, and in the Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) clinical practice guidelines the recommendation is to call these patients health care–associated pneumonia (HCAP) patients, because of the similarity to pneumonia acquired in the hospital setting (hospital-acquired pneumonia or ventilator-associated pneumonia). We limit our review to CAP only, and do not include HCAP studies; however, we consider prior antibiotic therapy as a risk factor for resistant pneumococcal disease. Advanced age has been associated with risk for acquiring severe CAP, particularly for those in whom comorbid conditions are also present. It is important to highlight the recent evidence associated with certain comorbid conditions, such as chronic obstructive pulmonary disease (COPD), alcohol abuse, renal failure, chronic heart failure, diabetes mellitus, coronary artery disease, malignancy, chronic neurologic disease, and chronic liver disease. In the past few years, there has been interest in identifying certain risk factors associated with mortality even in patients who do not have comorbid conditions. These risk factors include signs of disease progression, multilobar lung disease, need for mechanical ventilation, and need for vasopressors. In addition, these patients have the greatest severity of the disease, which leads to higher mortality.

MICROBIOLOGY

Multiple studies have evaluated the microbiology of patients who have severe CAP. Despite extensive laboratory testing, however, the causative pathogen remains unknown in 40% to 70% of cases. It is estimated that the recognition of causative
Severe Community-Acquired Pneumonia

Pathogens is higher in patients who have severe CAP, possibly because the laboratory testing is more available and there is a tendency toward higher testing in higher acuity levels. The most commonly recognized pathogen identified by far in ICU patients who have CAP is *Streptococcus pneumoniae*. Other respiratory tract pathogens associated with CAP in the ICU include *Haemophilus influenzae, Klebsiella pneumoniae, Legionella* spp, *Staphylococcus aureus*, and viral pneumonias. Mixed infections with typical and atypical pathogens occur in approximately 5% to 40% of cases and should always be considered to ensure patients are treated with appropriate empiric antimicrobial therapy. The most common pathogens implicated with lethality are *S pneumoniae, S aureus* (particularly the community-associated methicillin-resistant strain CA-MRSA), *Legionella pneumophila, and Pseudomonas aeruginosa*. Extensive interest has focused on patients who have CAP due to drug-resistant *S pneumonia* (DRSP). Multiple studies were not able to confirm the association of DRSP and poor clinical outcomes. Rates of pneumonia due to *S aureus* have been increasing in the past 2 decades. Community-acquired MRSA pneumonia has been linked as a secondary bacterial infection in patients who have influenza infection. Consequently, the Centers for Disease Control and Prevention has recommended empirically covering for MRSA in community-dwelling hosts who present with this viral infection. *P aeruginosa* has been reported in patients who have severe CAP with specific risk factors, such as chronic or prolonged use of broad-spectrum antibiotic therapy, bronchiectasis, malnutrition, HIV, and immunosuppression.

Table 1 shows the most common pathogens associated with severe CAP and their associated comorbid conditions.

**SEVERITY ASSESSMENT AND CRITERIA FOR ICU ADMISSION**

The site-of-care decision is critical for patients who have CAP because it affects the diagnostic work-up, the therapeutic interventions, and the clinical outcomes. Significant interest has been generated in this area of research over the past decade. In addition to the clinical prediction tools, there has been significant interest in the role of biomarkers as prognostic indicators in severe CAP. Several biomarkers have been suggested, but only few have enough clinical data to come up with substantial conclusions; the details go beyond the aims of this article and are therefore only briefly mentioned. The two better biomarkers currently available are the C-reactive protein (CRP) and procalcitonin (PCT). Procalcitonin was superior to CRP to predict CAP from other conditions, and in one study was significantly related to the severity of disease.

Several tools have been developed to predict mortality and accurately determine which patients could be sent home and treated safely with good clinical outcomes. Two extensively studied and validated tools have been recognized and are recommended by the multiple clinical practice guidelines related to CAP (Table 2). The pneumonia severity of illness (PSI) score and the CURB-65 are the most frequently cited scores. The PSI is based on 20 parameters that are evaluated at the time of clinical presentation and consist of three demographic, five comorbid conditions, five physical examination findings, and seven laboratory/imaging variables. The goal of this tool is to identify patients who can be discharged safely and receive home treatment with antibiotic therapy. The PSI score is heavily influenced by age, and it does not include certain comorbid conditions that are frequently found in patients who have CAP, such as diabetes and COPD. In contrast, the second score is less complex; it is derived from the original CURB, but the addition of age converted it to a six-variable tool that includes Confusion, Urea, Respiratory rate, Blood pressure, and older than 65 years of age (CURB-65). A simplified tool was suggested withdrawing
the only laboratory value needed to calculate the score (blood urea nitrogen) and named CRB-65, and it was validated with similar results.41 The CURB-65 score does not recognize any comorbid conditions previously associated as risk factors for CAP, however, and it does not include low oxygen levels as one of the criteria. We therefore conclude that these tools are good to determine low-risk patients, but should not be extrapolated to the other end of the spectrum, the high-risk group of patients. Several studies try to determine which patients should be admitted to the ICU. To evaluate this, the ATS developed initial criteria to define the need for ICU admission based on the original studies by Ewig and colleagues.42,43 Several changes were made to the initial criteria over the years, particularly in the minor criteria section. The most recent definition for severe CAP was suggested by the IDSA/ATS CAP guidelines in 2007.24 These guidelines recommend the need for ICU admission for those patients who have one of the major criteria (mechanical ventilation with endotracheal intubation or septic shock requiring vasopressors) or for patients who have three of the nine minor criteria (Table 3). Several studies have validated these criteria to admit patients to the ICU and applied them also in other groups of patients, including elderly and HIV-infected patients.5,37,42–46 The use of clinician experience and clinical judgment is always recommended in addition to the objective criteria.47

Several other tools have been evaluated to better predict the need for ICU admission and the risk for death in the highest severity group. Tools such as the

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>Smoking, COPD, low socioeconomic status, sulfur dioxide air pollution, alcoholism, dementia, seizures, congestive heart failure, CVD, HIV infection</td>
</tr>
<tr>
<td>DRSP</td>
<td>Alcoholism, β-lactams within 3 months, presence of more than one coexisting disease, immunosuppressive illness</td>
</tr>
<tr>
<td><em>GNB and Pseudomonas aeruginosa</em></td>
<td>Diabetes mellitus, decreased functional status, comorbidities (cardiopulmonary, renal, central nervous system, hepatic, neoplasia), chronic aspiration, bronchiectasis</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>Decreased functional status, CVD, intravenous drug use, diabetes mellitus, renal failure, influenza</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>Bronchiectasis</td>
</tr>
<tr>
<td>CA-MRSA</td>
<td>Skin infections and prior influenza infection</td>
</tr>
<tr>
<td><em>Legionella spp</em></td>
<td>Chronic steroid use, hematologic malignancy, humid weather, male sex, smoking, diabetes mellitus, cancer, ESRD, HIV infection</td>
</tr>
<tr>
<td>Influenza</td>
<td>Air pollutants (nitrogen oxide, ozone, and particulate matter), winter season</td>
</tr>
<tr>
<td>Anaerobes</td>
<td>High dental plaque index or periodontal disease, aspiration</td>
</tr>
</tbody>
</table>

**Abbreviations:** CA-MRSA, community-associated methicillin-resistant *S aureus*; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; DRSP, drug-resistant *S pneumoniae*; ESRD, end-stage renal disease; GNB, gram negative bacilli.
PS-CURXO80, SMART-COP, and the PIRO-CAP scores have been created for this purpose. España and colleagues\textsuperscript{48} developed and validated a clinical prediction rule to assess the diagnosis of severe CAP. This new prediction score was derived from the variables associated with severe CAP that include: arterial pH less than 7.30, Systolic blood pressure less than 90 mmHg, Confusion (or altered mental status), blood Urea nitrogen greater than 30 mg/dL, Respiratory rate greater than 30 breaths/min, multilobar/bilateral lung infiltrates (by X-ray), Oxygen arterial pressure less than 54 mm Hg or ratio of arterial oxygen tension to fraction of inspired oxygen less than 250 mm Hg, and age 80 years or older. The evaluation of severe CAP is based on the presence of one major criterion (PS) or two or more minor criteria (CURXO80). The model showed an area under the curve of 0.92 to accurately predict severe CAP\textsuperscript{48}.

Charles and colleagues\textsuperscript{49} developed the SMART-COP to predict the need for intensive respiratory and vasopressor support. The features statistically significantly associated with receipt of intensive respiratory care or vasopressor support were low Systolic blood pressure (1 point), Multilobar chest radiography involvement (1 point), low Albumin level (1 point), high Respiratory rate (age-adjusted) (1 point), Tachycardia (1 point), Confusion (1 point), poor Oxygenation (age-adjusted) (2 points), and low arterial pH (< 7.35) (2 points): SMART-COP. A SMART-COP score of 3 points or more identified 92% of patients who received intensive respiratory care or vasopressor support, including 84% of patients who did not need immediate admission to the ICU. This tool was validated externally in five different cohorts with consistent results and can assist the clinician in assessing the need for intensive respiratory care or vasopressor support and CAP severity.

### Table 2

<table>
<thead>
<tr>
<th>Pneumonia Severity Index Score\textsuperscript{a}</th>
<th>CURB-65\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk Class</strong></td>
<td><strong>Points</strong></td>
</tr>
<tr>
<td>I</td>
<td>— \textsuperscript{c}</td>
</tr>
<tr>
<td>II</td>
<td>&lt;70</td>
</tr>
<tr>
<td>III</td>
<td>71–90</td>
</tr>
<tr>
<td>IV</td>
<td>91–130</td>
</tr>
<tr>
<td>V</td>
<td>&gt;130</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Metlay and Fine\textsuperscript{47} suggested a three-step process to decide the initial site of CAP treatment based on: (1) assessment of preexisting conditions that compromise safety of home care, (2) calculation of the pneumonia severity index score, and (3) clinical judgment\textsuperscript{48}. Data from Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med 1997;336:243–50.

\textsuperscript{b} CURB-65\textsuperscript{40,41} related to Confusion (altered mental status); serum blood Urea nitrogen > 19.6 mg/dL; Respiratory rate > 30 breaths per minute; Blood pressure (BP) (systolic BP < 90 mm Hg or diastolic BP < 60 mm Hg); and age \textgreater 65 years. Each criterion has a score of one, and the total score is added by the presence of each of the five criteria. Two or more criteria suggest severe CAP and admission to the hospital is recommended; a patient who has three or more criteria needs an assessment for ICU (more likely to be in scores 4 or 5).

\textsuperscript{c} Risk class I: age < 50 years, no comorbidities, and absence of vital sign abnormalities.
Rello and colleagues developed the CAP-PIRO score based on the score suggested for the risk for sepsis. This score evaluates variables related to the PIRO score that include: Predisposition, Infection, Response, and Organ dysfunction. The CAP-PIRO score intends to adjust for the complexity of the patients critically ill with CAP. CAP-PIRO score evaluates the following variables: Predisposition: comorbidities (COPD or immunocompromised) (1 point), age greater than 70 years (1 point); Infection: bacteremia (1 point), multilobar opacities (1 point); Response: shock (1 point), severe hypoxemia (1 point); and Organ dysfunction: acute respiratory distress syndrome (ARDS, 1 point), acute renal failure (1 point). Considering the observed mortality from each PIRO score, the patients were stratified in four levels of risk: (a) low, 0 to 2 points; (b) mild, 3 points; (c) high, 4 points; and (d) very high, 5 to 8 points. This score was able to consistently predict the ICU mortality and health care use in a cohort of 529 patients admitted to the ICU with CAP.

In conclusion, the last four severity criteria scores have in common the overlap in the variables selected, and it is clear that the new concept of severe CAP goes beyond the lungs and looks for systemic organ dysfunction (Table 4). Future prospective validation studies are needed for these scores.

THERAPEUTIC STRATEGIES TO MANAGE SCAP PATIENTS

Traditionally the antimicrobial agents have been considered the cornerstone of therapy against severe CAP; however, with the purpose of understanding severe CAP as a systemic disease, there are other non-antimicrobial therapies that should be considered in this group of patients. Therapeutic strategies for managing patients who have severe CAP are summarized in Box 1.

Antimicrobial Therapies

Several professional organizations developed clinical practice guidelines with the objective of standardized therapy for CAP following an evidence-based medicine
approach. The guidelines include specific recommendations for patients who have severe CAP usually managed in the ICU. If a patient has no risk factors for pseudomonas infection, the treatment should include two antibiotics, one (β-lactam) that covers pneumococcus (including drug-resistant isolates) and other likely respiratory pathogens, and therapy against atypical pathogens, especially *Legionella* spp, such as a macrolide (azithromycin or clarithromycin) or a respiratory fluoroquinolone (levofloxacin the highest dose of 750 mg/d or moxifloxacin). If there are risk factors for *P aeruginosa*, the treatment should include at least three antibacterial medications: an initial empiric combination of appropriate antipseudomonal coverage (with a β-lactam antipseudomonal therapy) plus an antipseudomonas fluoroquinolone (levofloxacin 750 mg/d or ciprofloxacin 400 mg three times a day) or an antipseudomonal aminoglycoside. The downside of a combination with an aminoglycoside is that atypicals, particularly *Legionella*, are not covered by this approach. In addition, the guidelines recommend including an antimicrobial agent with activity against atypical pathogens (eg, *L pneumophila*), using a regimen that includes a fluoroquinolone or, if fluoroquinolone is not present, the association of a macrolide. The failure to identify a pathogen has not been associated with a worse outcome particularly in the severely ill, but the empiric regimen should cover *S pneumoniae* and atypical pathogens. In conclusion, the recommendation is to use empiric combination therapy with two or more antimicrobial agents according to the risk for pseudomonas infection and the constant atypical coverage mainly for legionella infection.

The data regarding the use of combination therapy are limited to a few randomized controlled trials, and most of the data come from observational studies that have evaluated the benefit of using combination therapy versus monotherapy in patients who have severe CAP admitted to the ICU. From the limited data and significant heterogeneity between studies, we conclude that limited information is available to support the use of antimicrobial monotherapy in patients who have CAP in the ICU and further randomized controlled trials should be performed to clarify these questions.

Of all the combinations recommended by the guidelines, the one that has acquired a critical role is the use of macrolides in association with other antimicrobials. Initially, Waterer and colleagues found that single effective drug therapy for severe bacteremic pneumococcal pneumonia was associated with a greater risk for death than dual effective therapy. Several other studies suggested a benefit to having a macrolide added to the β-lactam therapy in patients who have bacteremic pneumococcal pneumonia. Not adding a macrolide to a β-lactam–based initial antibiotic regimen was an independent predictor of in-hospital mortality. Recent studies suggest that macrolides may have beneficial effects for patients at risk for certain infections because of their immunomodulatory effects rather than antimicrobial properties. In addition to these observations about noninfectious diseases, macrolides have been associated with better clinical outcomes in bacteremic pneumococcal pneumonia, CAP, and ventilator associated pneumonia. Rodriguez and colleagues found that in the subset of ICU patients who had CAP and shock, combination antibiotic therapy improved survival rates (odds ratio [OR] = 1.69; 95% CI, 1.09–2.60; *P* = .01), suggesting that combination therapy may be beneficial in more severe cases. This effect is presumed to be secondary to the immunomodulatory effect rather than the antimicrobial effects, particularly associated with the host inflammatory response.

On the other hand, there is enough clinical evidence that supports the clinical practice guideline recommendations by demonstrating statistically significant
### Table 4
Summary of variables evaluated by the different scoring systems to identify patients who have severe community-acquired pneumonia

<table>
<thead>
<tr>
<th>IDSA/ATSA 2007 (Minor Criteria)</th>
<th>PS CURXO80</th>
<th>SMART-COP</th>
<th>CAP PIRO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>≥ 80 y</td>
<td>—</td>
<td>Age &gt; 70 y</td>
</tr>
<tr>
<td><strong>Neurologic dysfunction</strong></td>
<td>New-onset confusion/disorientation</td>
<td>Confusion</td>
<td>Confusion</td>
</tr>
<tr>
<td><strong>Respiratory dysfunction</strong></td>
<td>Respiratory rate ≥ 30 bpm</td>
<td>Respiratory rate &gt; 30 breaths/min</td>
<td>High respiratory rate (age-adjusted)</td>
</tr>
<tr>
<td></td>
<td>PaO₂/FIO₂ ratio ≤ 250</td>
<td>PaO₂/FIO₂ ratio ≤ 250&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Poor oxygenation (age-adjusted)</td>
</tr>
<tr>
<td><strong>Circulatory dysfunction</strong></td>
<td>Hypotension requiring aggressive fluid resuscitation</td>
<td>Systolic blood pressure &lt; 90 mm Hg</td>
<td>Systolic blood pressure &lt; 90 mm Hg</td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>—</td>
<td>Shock</td>
</tr>
<tr>
<td><strong>Renal dysfunction</strong></td>
<td>Uremia (BUN level &gt; 20 mg/dL)</td>
<td>BUN &gt; 30 mg/dL</td>
<td>—</td>
</tr>
<tr>
<td><strong>Hematologic dysfunction</strong></td>
<td>Leukopenia (WBC count &lt; 4000 cells/mL)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Metabolic dysfunction</td>
<td>Arterial pH &lt; 7.30</td>
<td>—</td>
<td>Arterial pH &lt; 7.35</td>
</tr>
<tr>
<td>-----------------------</td>
<td>--------------------</td>
<td>---</td>
<td>-------------------</td>
</tr>
<tr>
<td>Nutritional dysfunction</td>
<td>—</td>
<td>—</td>
<td>Low albumin level</td>
</tr>
<tr>
<td>Temperature</td>
<td>Hypothermia (core temperature &lt; 36°C)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Chest radiograph findings</td>
<td>Bilateral or multilobar infiltrates</td>
<td>Multilobar/bilateral lung affection</td>
<td>Multilobar chest radiography involvement</td>
</tr>
<tr>
<td>Laboratory</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Severe criteria (need for mechanical ventilation or septic shock with the need for vasopressors) by the 2007 IDSA/ATS were excluded from this table because there are no other places to care for these patients who have severe CAP.

a Hypoxemia: oxygen arterial pressure < 54 mm Hg or PaO₂/FIO₂ < 250 mm Hg.
benefit for those patients receiving guideline-concordant therapies in patients who have CAP. In addition, there are data to support the benefit of using a combination therapy of β-lactam agent plus a macrolide for initial empiric therapy to reduce mortality in patients who have CAP. National practice guidelines strongly recommend that locally adapted guidelines should be implemented to improve process of care variables and relevant clinical outcomes. Adherence to clinical practice guidelines for the treatment of CAP improves quality and efficiency of care. Several studies report the use of a critical pathway to improve the treatment of CAP patients, including those who have severe disease. Other publications have consistently found a decrease in mortality with the introduction of guideline-concordant antimicrobial therapy or guideline-based protocols. Several of the quality indicators—early administration of antibiotics, appropriate antibiotic use following the clinical practice guidelines, use of a critical pathway, switch to oral therapy and early discharge—have all shown improved clinical outcomes in CAP.

Non-Antimicrobial Therapies

Other non-antimicrobial therapies have focused on supporting patients who have evidence of severe CAP or sepsis due to CAP in a more comprehensive approach. These interventions are directed to early supportive therapy for patients who have severe sepsis correlating with improved survival, such as systemic corticosteroid therapy, lung protective-ventilation strategy, and recombinant human-activated protein C for severe sepsis.

Systemic steroids as adjunct therapy

Previous studies have shown increased pulmonary and systemic inflammatory cytokine levels in patients who have severe CAP. Among ICU patients higher circulating inflammatory cytokine levels correlate with the presence of bilateral pneumonia, need for mechanical ventilation, and higher Acute Physiology and Chronic Health Evaluation (APACHE) II and Multiple Organ Dysfunction Syndrome scores. A balance between pro- and anti-inflammatory cytokines is critical in the host response. A randomized controlled trial evaluated the efficacy and safety of 7 days of low-dose hydrocortisone infusion in 46 patients who had severe CAP admitted to the ICU. They found significant reduction in mortality (hydrocortisone group 0% versus placebo group 30%, \( P = .009 \)) and length of ICU stay.
(hydrocortisone group 10 days versus placebo group 18 days, \( P = .01 \)). A retrospective study\(^9\) that included 308 patients who had severe CAP (PSI classes IV and V) found that treatment with systemic steroids reduced mortality in the cohort of patients who had severe pneumonia (OR = 0.29; 95% CI, 0.11–0.73). The encouraging results of Confalonieri and colleagues\(^9\) and Garcia-Vidal and colleagues\(^9\) suggest that the effects of systemic steroid administration as immunomodulating agents in an immunocompetent host who has severe CAP can decrease mortality. Several ongoing randomized controlled trials may clarify this area of research in the near future.

Recombinant human activated protein C or drotrecogin alfa (activated)

CAP is the leading cause of severe sepsis.\(^9\) Angus and colleagues\(^9\) found that respiratory infections were 44% of severe sepsis cases in a cohort of 192,980 patients. In a recent study that included 1339 patients hospitalized for CAP, Dremsizov and colleagues\(^9\) reported that severe sepsis developed in 48% of the patients. Activated protein C is an important modulator of inflammation and coagulation in sepsis. Bernard and colleagues\(^9\) reported a randomized controlled trial of 1690 adult patients who had severe sepsis (at least one organ failing within the first 24 hours of evaluation) in whom drotrecogin alfa (activated) was evaluated for clinical efficacy and safety. They found a mortality rate of 24.7% with drotrecogin alfa (activated) compared with 30.8% in the placebo group (\( P = .005 \)), with an absolute risk reduction of death of 6.1%.\(^9\) Severe bleeding episodes (defined as intracranial hemorrhage, any life-threatening bleeding, any bleeding classified as serious by the investigator, or any bleeding that required the administration of at least three units of packed red blood cells on two consecutive days) occurred in 3.5% of patients receiving drotrecogin alfa (activated) compared with 2.0% of patients receiving placebo (\( P = .06 \)). A post hoc analysis by the Food and Drug Administration (FDA) of data from this study suggested that the reduction in mortality was restricted to patients who had APACHE II scores of 25 or more.\(^9\) In the PROWESS trial the lung was the most common site of infection (53.6%), and 73% of patients in the treatment group and 77% in the placebo group required mechanical ventilation.\(^9\) Laterre and colleagues\(^9\) in a secondary analysis of the severe CAP subgroup in the PROWESS trial found that 35.6% of the 1690 patients were classified as severe CAP. Of these, 26.1% had \( S \) pneumoniae infections. In patients who had severe CAP who received drotrecogin alfa (activated), there was a relative risk (RR) reduction in mortality of 28% (RR = 0.72; 95% CI, 0.55–0.94) at 28 days and 14% (RR = 0.86; 95% CI, 0.69–1.07) at 90 days. The survival benefit was most pronounced in patients who had severe CAP with \( S \) pneumoniae and in patients who had severe CAP at high risk for death as indicated by APACHE II score greater than 25, PSI score greater than 4, or CURB-65 score greater than 3.\(^9\) These results, although not definitive, suggest that severe sepsis due to CAP may be responsive to drotrecogin alfa (activated) treatment, and might be considered on a case-by-case basis when treating patients who have severe sepsis resulting from CAP.\(^9\) The administration of drotrecogin alfa (activated) in Early Stage Severe Sepsis (ADDRESS) trial, with patients who had less severe sepsis and a low risk for death (as defined by APACHE II scores < 25 or single-organ failure) show no impact on clinical effect with a similar rate of bleeding as a prior report.\(^9\)

The IDSA/ATS CAP guidelines\(^2\) and the new Surviving Sepsis Campaign guidelines\(^9\) suggest that drotrecogin alfa (activated) should be considered for treatment of patients who have CAP within 24 hours of admission if they are in the subgroup of high risk for death: APACHE II scores of 25 or greater or multiple organ failure. Two randomized control trials were requested by the FDA to confirm these prior findings, however, and until the final results of these trials are available we recommend...
a case-by-case selection of patients who have severe sepsis who may benefit from this treatment.

**Lung protective-ventilation strategy**

CAP was the most common cause of ARDS in the ARDSNet trial.\(^{100}\) Two randomized controlled trials\(^{100,101}\) demonstrated that tidal volume (V\(_T\)) of 6 mL/kg predicted body weight (PBW) results in better outcomes than V\(_T\) of 12 mL/kg PBW in patients who have acute lung injury (ALI)/ARDS. The ARDSNet trial\(^{100}\) showed that low V\(_T\) (6 mL/kg PBW) had a mortality of 31% when compared with higher V\(_T\) (12 mL/kg PBW) 40% mortality (\(P = .007\)). The absolute risk reduction for mortality in the pneumonia subgroup was 11%.\(^{102}\) The IDSA/ATS guidelines recommend the use of a lung protective-ventilation strategy (with low V\(_T\) 6–8 mL/kg PBW and plateau pressure goal ≤ 30 cm H\(_2\)O) in patients who have ALI/ARDS, including those who have severe CAP.

**COMMUNITY-ACQUIRED PNEUMONIA BUNDLE**

The greatest opportunity to improve patient outcomes will probably come not from discovering new treatments but from the effective delivery of existing evidence-based therapies.\(^{103}\) The bundle is a series of interventions or processes related to care of patients that, when implemented together, will achieve significantly better outcomes than when implemented individually. The components that make up the bundle have to be grounded by an extensive research base.\(^{104}\) The components of the CAP bundle have shown an impact on clinical outcomes of patients who have CAP.\(^{15,105}\) We concur with the experts\(^{24,26}\) that an early CAP bundle should include a series of processes of care\(^{15}\) in the management of CAP: (1) time to pulse oximetry monitoring (< 3 hours), (2) time to arterial blood gas sampling (in less than 3 hours from presentation), (3) time to blood culture sampling (before the first antibiotic dose), (4) time to first antibiotic dose within 4 to 8 hours (first 6 hours of presentation to the emergency department) of presentation or at least while still in the emergency room, (5) guideline-concordant antibiotic therapy, (6) collection of mortality data (PSI or CURB-65) for all patients who have CAP admitted, and (7) determination of what percentage of at-risk patients receive immunization for influenza or pneumococcal infection. This bundle allows the clinician to identify patients at risk for worst clinical outcomes in which an early and appropriate intervention will likely improve the outcomes of patients who have severe CAP.

**SUMMARY**

Severe CAP is a complex condition with significant morbidity, mortality, and health care cost. The use of risk stratification is important to better define which patients require a more intensive level of care and a more comprehensive approach. Appropriate antibiotic therapy with early initiation of combination therapy is an important component in the management of patients who have CAP in the ICU. Ideally, current approaches regarding the treatment of patients who have severe CAP are focused on combining conventional antibiotic therapy with early supportive non-antimicrobial therapies that may improve the outcomes of patients who have severe disease. Future research is needed in these areas, so that the risks for treatment failure, morbidity, mortality, and cost due to severe CAP may be minimized.

**REFERENCES**


55. Fogarty C, Siami G, Kholer R, et al. Multicenter, open label, randomized study to compare the safety and efficacy of levofloxacin versus ceftriaxone sodium and


