Severe Community-Acquired Pneumonia

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Abstract

Severe community-acquired pneumonia is a clinical diagnosis with significant impact on healthcare management around the world, with the highest morbidity and mortality of all the forms of community-acquired pneumonia. Severe pneumonia patients usually require intensive care unit management, including vasopressors and/or mechanical ventilation. Early clinical suspicion and prompt empiric antimicrobial therapies are mandatory in patients with severe pneumonia. A number of recent studies and guidelines addressing these issues have been published. They are reviewed in this article.

Introduction

Community-acquired pneumonia (CAP) is the sixth leading cause of death overall and is the most common cause of death from infectious diseases in the United States.^{1,2} Around half a million patients are hospitalized each year in the United States for treatment of CAP.³ CAP in severely ill patients requires intensive hospital care in the intensive care unit (ICU). These patients carry the highest mortality rates of all patients with CAP.⁴ The guidelines of the American Thoracic Society (ATS),⁵ the European Respiratory Society (ERS),^{6,7} the Canadian Infectious Diseases Society (CIDS), the Canadian Thoracic Society (CTS),⁸ the Infectious Society of America (IDSA),⁹ and the Centers for Disease Control and Prevention (CDC)¹⁰ agree in that severe CAP represents a unique pneumonia syndrome that requires a distinct approach. The purpose of this chapter is to review the current literature with regard to severe CAP—the definition, criteria for admission to the ICU, epidemiologic factors, etiology, clinical outcomes, prognosis, and therapeutic regimens.

Definition and Criteria For ICU Admission

Severe CAP is defined as the clinical syndrome of severely ill patients with pneumonia requiring ICU admission.⁵ The patients with severe CAP have

been separated from cases of less severe pneumonia requiring hospitalization because of the high mortality rate (up to 50%).⁵ The decision to hospitalize patients with CAP is one of the most critical for the physician treating a patient with CAP.¹¹ Several studies of CAP severity of illness have developed prediction rules to determine the site of care for patients with CAP and the need for ICU admission.^{12–15}

Risk Score Assessment

Fine and colleagues¹² developed a pneumonia-specific severity of illness (PSI) score as part of the pneumonia Patient Outcome Research Team (PORT) study. The 20 items included three demographic variables, five comorbid conditions, five physical examination findings, and seven laboratory/imaging results. For each variable present, points are added to the score, and this final score is then broken into five risk classes. Those patients in risk classes I to III are at low risk and can be managed as outpatients, with a mortality rate of less than 1%. However, those patients with risk classification IV had a 9% mortality rate, and class V patients had a 27% mortality rate. The study suggested that patients in classes IV and V might require hospitalization. Although the study did not specifically evaluate the need for ICU admission, patients in class V were more likely to require ICU admission.

Marrie et al¹³ conducted a randomized evaluation of a critical pathway for managing pneumonia⁹ (hospitals in the critical pathway group versus 10 hospitals in the conventional management group) in 19 Canadian teaching and community hospitals. The PSI was used to assist with the site of care decision. The critical pathway reduced the use of institutional resources (fewer bed days per patient managed and decrease in the admission of low-risk patients) with no differences in the rates of complications, readmission, or mortality.

Severity Criteria Assessment

The ATS criteria included patients with severe CAP and divided the nine criteria into five “minor” criteria that could be present on admission and four “major” criteria that could be present on admission or later in the hospital stay (Table 4.1).^{5,14} In this prospective study, Ewing et al.¹⁵ reported on 422 consecutive patients with CAP, 64 of whom were admitted to the ICU. The need for ICU admission was defined by a rule that required the presence of at least two or three minor criteria [systolic blood pressure (BP) $\leq$ 90 mmHg, multilobar disease, $\text{PaO}_2/\text{FIO}_2 < 250$], or one of two major criteria (need for mechanical ventilation or septic shock). This rule demonstrated a sensitivity of 78%, specificity of 94%, positive predictive value of 75%, and negative predictive value of 95%.

The British Thoracic Society (BTS) added mental status changes (confusion) and blood urea nitrogen (BUN) >19.6 mg/dl to the preceding set of

Table 4.1. Severity Criteria for Severe Community-Acquired Pneumonia

Minor Criteria ($n = 5$)	Major Criteria ($n = 4$)
Respiratory rate $\geq 30/\text{min}$ $\text{PaO}_2/\text{FIO}_2 < 250^\dagger$	Need for mechanical ventilation* Increase in the size of infiltrates by $> 50\%$ within 48 h
Bilateral pneumonia or multilobar pneumonia [†]	Acute renal failure (urine output $< 80 \text{ mL}$ in 4 h or serum creatinine $> 2 \text{ mg/dL}$ in the absence of chronic renal failure)
Systolic BP $\leq 90 \text{ mm Hg}^\dagger$ Diastolic BP $\leq 60 \text{ mm Hg}$	Septic shock or the need for pressors for $> 4 \text{ h}^*$

* Either one of two major criteria.

† Either two of three minor criteria.

(Data from references 5, 14, 15.)

criteria.¹⁶ Cordero et al¹⁷ validated the ATS severity criteria in human immunodeficiency virus (HIV)–infected patients. The severity assessment criteria are important in helping physicians identify patients who need hospitalization or ICU admission, but they are not meant to remove physicians' clinical judgment in the decision-making process.

Etiology

The most common organisms in patients with severe CAP are *Streptococcus pneumoniae*, *Legionella* spp., *Haemophilys influenzae*, *Staphylococcus aureus*, and Gram-negative bacilli (GNB) (Table 4.2)^{4,17–23} From this group of microorganisms, *S. pneumoniae* is the most frequent causative agent, followed by *Legionella* spp. and gram-negative rods. *S. pneumoniae* is present in up to one-third of all ICU patients.^{4,17–23} Atypical microorganisms such as *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and some viruses are considered to be copathogens but are not usually the cause of severe CAP.^{22–26} Viral pneumonias resulting in community outbreaks of influenza, respiratory syncytial virus (RSV), and para-influenza can be life-threatening in elderly and immunocompromised patients.^{4,18,20,22,24,26} Influenza pneumonia may be complicated by direct involvement of the lung parenchyma or by secondary bacterial infection due to *S. pneumoniae*, *S. aureus*, *H. influenzae*, or other Gram-negative pathogens.²⁴ Sin Nombre hantavirus (SNV) may present as acute respiratory failure requiring ICU admission and mechanical ventilation and is associated with a high mortality rate.²⁵ The CDC and the World Health Organization recently reported a multicountry outbreak of severe respiratory syndrome (SARS).^{28,29} Infection with a novel coronavirus has been implicated as the possible cause of SARS.³⁰ All these patients have fever and respiratory symptoms (e.g., nonproductive cough, shortness of breath, and radiographic evidence of pneumonia). The case fatality rate is 3.9% and is mainly in elderly and immunocompromised subjects.^{31–33}

Table 4.2. Etiologic Agents in ICU Patients with Severe Community-Acquired Pneumonia

Common	Rare
<i>Streptococcus pneumoniae</i> (including drug-resistant <i>Streptococcus pneumoniae</i> —DRSP)	<i>Chlamydia pneumoniae</i> and <i>C. psittaci</i>
<i>Legionella</i> spp.	<i>Coxiella burnetii</i>
<i>Haemophilus influenzae</i>	Respiratory viruses, coronavirus
Enteric Gram-negative bacilli (especially <i>Klebsiella</i> spp.)	Endemic fungi (coccidioidomycosis, histoplasmosis, blastomycosis) [†]
<i>Staphylococcus aureus</i>	<i>Streptococcus pyogenes</i>
<i>Mycoplasma pneumoniae</i>	<i>Mycobacterium tuberculosis</i>
<i>Pseudomonas aeruginosa</i> *	<i>Pneumocystis carinii</i> [†]
	Coronavirus (SARS)

* *Pseudomonas aeruginosa* is suspected in patients with bronchiectasis.
† *Pneumocystis carinii* pneumonia and endemic mycosis are seen in patients with underlying immunosuppression (HIV/AIDS, steroid use, etc.).
(Data from references 4, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28.)

P. aeruginosa has been reported in severe CAP patients with specific risk factors, such as chronic or prolonged broad-spectrum antibiotic therapy, bronchiectasis, malnutrition, HIV, and immunosuppression.^{5,17,21} Endemic mycosis, *Mycobacterium tuberculosis*, and *Pneumocystis carinii* pneumonia deserve to be mentioned here, although they are usually excluded from CAP guidelines.^{5,9} These pathogens should be suspected in immunocompromised patients presenting to the ICU with severe CAP. Mixed infections occur in about 10% to 20% of all cases and should always be suspected, to ensure that patients are treated with appropriate empiric antimicrobial therapy.^{5,8,9} In all series, about 40% to 70% of patients with severe CAP have no pathogen identified.^{17–23} The failure to identify a pathogen has not been associated with a worse outcome.^{34,35}

Epidemiology

Around 10% of all hospitalized patients require ICU admission.^{28–30} The recommendations for hospitalization and for ICU admission were described earlier. Roson et al⁴ prospectively collected data on 533 nonseverely immunosuppressed patients with CAP. Of these, 303 patients (60%) were classified in PSI risk classes IV and V, with a mortality rate of up to 29%. One of the most important determinants in patients with severe CAP is the patient’s chronic comorbid condition.^{4,19,20,22,23,26} The most common comorbid illnesses are chronic obstructive pulmonary disease, which is present in up to one-half of the patients, followed by alcoholism, chronic heart disease, and diabetes mellitus (Table 4.3).^{4,19,20,22,23,26} Approximately one-third of patients with se-

Table 4.3. Comorbid Illness Associated with Severe Community-Acquired Pneumonia

Common	Other
Chronic obstructive pulmonary disease (COPD, severe asthma, or bronchiectasis)	Inappropriate initial ambulatory or in-hospital antimicrobial treatment
Chronic heart disease (congestive heart failure, ischemic cardiopathy, valvular disease, or cardiomyopathy)	Immunosuppression (neoplasias, HIV infection, corticosteroid treatment)
Renal failure	Malnutrition
Neurologic diseases	Gross aspiration
Alcoholism	Hepatic disease
Diabetes mellitus	Bacteremia
Age	Smoking history (>4 pack-years)
Nursing home residents	(ref. 22)

(Data from references 4, 19, 20, 22, 23, 26.)

vere CAP were previously healthy.²⁶ Elderly and nursing home patients are also at significant risk for CAP and have high mortality rates.³⁷

Outcome and Prognosis

Several studies recently published by Moroney et al,³⁸ Kalin et al,³⁹ and Metlay et al⁴⁰ evaluated clinical outcomes in patients with bacteremic pneumococcal pneumonia. Antimicrobial resistance in *S. pneumoniae* showed no contribution to mortality or requirement for ICU admission but may be associated with an increased risk of adverse outcome such as suppurative complications of infection.³⁸⁻⁴⁰ Causes of death principally included refractory hypoxemia, refractory shock, and other pneumonia-related complications, predominantly multiorgan failure.^{18,41} Mortality rates and risk factors associated with mortality by multivariate analysis are reported in Table 4.4.^{4,20,22}

Treatment

Antimicrobial Treatment

Several professional organizations have developed treatment guidelines to standardize therapy for CAP, including severe CAP. During the past year the ATS,⁵ CIDS and CTS,⁸ IDSA,⁹ and CDC¹⁰ published updated, extensive guidelines that reflect the evolution of opinion regarding CAP management in immunocompetent adults. All these guidelines support the idea that treatment of patients with severe CAP should focus on the possible associated etiologic agents. Empiric treatment with combination antimicrobial therapy

Table 4.4. Risk Factors Associated with Mortality by Multivariate Analysis in Patients with Severe Community-Acquired Pneumonia

Reference	Risk Factors for Mortality	Mortality %
Roson et al.	History of neoplasia, respiratory failure, renal failure, decreased level of consciousness, shock, and a simplified acute physiology score of > 10	10–29
El-Solh and coworkers	Multilobar involvement, septic shock, decrease in 24-hour urine output, and inadequate antimicrobial therapy	54.8
Luna et al.	PaO ₂ /FIO ₂ < 250, aerobic Gram-negative pathogen, chronic renal failure, Glasgow score < 15, malignant neoplasm, and aspiration	40

(Data from references 4, 20, 22).

should be initiated, preferably within the first 4 hours of presentation and at least within the first 8 hours of admission.⁹ Empiric therapy should be directed against pneumococcus, *H. influenzae*, and Gram-negative bacilli with β -lactam medications or fluoroquinolones, and *Legionella* (and other atypicals) covered with macrolide or fluoroquinolone (Table 4.5).^{5,8,9} In cases where the infecting pathogen can be identified, directed therapy should be employed. The most common empiric antibiotic regimen suggested includes a third-generation cephalosporin in combination with a macrolide or a fluoroquinolone.^{4,19,20,22} Patients with risk factors for *P. aeruginosa* should receive appropriate antipseudomonal agents.

Waterer et al.⁴² found that single effective drug therapy for severe bacteremic pneumococcal pneumonia was associated with a greater risk of death than dual effective therapy. Burgess and Lewis⁴³ performed a retrospective evaluation of 213 hospitalized (not ICU) patients with CAP and concluded that the addition of a macrolide to a nonpseudomonal third-generation cephalosporin as initial therapy for the treatment of CAP may not be necessary. However, Gleason et al.⁴⁴ showed in 12,945 Medicare inpatient (≥ 65 years of age) records that initial treatment for CAP with a second-generation cephalosporin plus macrolide, a nonpseudomonal third-generation cephalosporin plus macrolide, or a fluoroquinolone alone was independently associated with lower 30-day mortality in patients with a PSI class IV and V. More recently, Martinez et al.⁴⁵ confirmed these observation in an analysis of 409 *S. pneumoniae* bacteremic patients. The multivariant analysis revealed that in the initial treatment regimen the lack of inclusion of a macrolide in combination with a β -lactamic antibiotic was associated with increased hospital mortality.

Generally, the duration of therapy in patients with severe CAP is 7 to 10 days, but those with atypical pathogens such as *Legionella* spp. should receive longer treatment—10 to 14 days.⁵ Several studies report the use of a

Table 4.5. Empiric Antimicrobial Regimen to Treat Severe Community-Acquired Pneumonia

Empiric Treatment	Comments
Intravenous β -lactam Third-generation cephalosporins (ceftriaxone or cefotaxime)	Covers well <i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> , enteric Gram- negative bacilli (<i>Klebsiella</i> spp.)
or Beta-lactam/b-lactamase inhibitor (ampicillin-clavulanate or piperacillin-tazobactam)	* Fluoroquinolones also cover these pathogens, including DRSP.
plus either Intravenous macrolide (erythromycin or azithromycin)	<i>Legionella</i> spp., <i>Mycoplasma</i> <i>pneumoniae</i> , <i>Chlamydia</i> <i>pneumoniae</i> , and <i>C. psittaci</i>
or Intravenous fluoroquinolone* (levofloxacin, gatifloxacin, or moxifloxacin)	
Intravenous beta-lactam Antipseudomonal beta-lactam/ b-lactamase inhibitor (cefepime, piperacillin-tazobactam, imipenem, meropenem)	<i>Pseudomonas aeruginosa</i> (and the other pathogens above)
plus either Intravenous aminoglycoside or intravenous ciprofloxacin	
plus Intravenous macrolide (erythromycin or azithromycin) if aminoglycoside used, but not with ciprofloxacin	

(Data from references 5, 8, 9, 10.)

critical pathway to improve the treatment for CAP patients, including those with severe CAP.^{46–51} Antimicrobial treatment failures are usually underestimated. The most common causes include microbial resistance to the initial antimicrobial regimen, suppurative complications, or the presence of nosocomial pneumonia.⁵²

After the initial clinical improvement, hospitalized patients should be switched from IV antibiotic therapy to oral therapy, while continuing similar antimicrobial coverage that provides similar tissue concentrations as the parenteral counterpart. Criteria for determining when the patient can transition to oral antibiotics include the ability to tolerate antibiotics by mouth, a functioning gastrointestinal tract, stable blood pressure, decreasing white blood cell count, and improving symptoms such as cough, dyspnea, and fevers.^{5,53–55} A meta-analysis by Rhew et al.⁵⁵ evaluated early-switch and early-discharge strategies in patients with CAP with a significant and safe reduction of the mean length of stay.

Nonantimicrobial Treatment

Nonantimicrobial treatments include mechanical ventilation (invasive and noninvasive), vasopressor management of shock and hypotension, and immunomodulators.^{56,57} Mechanical ventilation by invasive and noninvasive mechanical ventilation (NIMV) have been used in severe CAP, with the main objectives of improving the significant hypoxemia and preventing the development of respiratory failure and adult respiratory distress syndrome (ARDS).^{58–60} NIMV is used with the goal of avoiding mechanical ventilation and reducing intubation rates in patients with comorbid conditions, with a shorter stay in the ICU and hospital.^{61–64} NIMV has been used for severe pneumonia in different populations with variable results, suggesting a benefit in immunocompromised patients with AIDS and *Pneumocystis carinii* pneumonia, and with hematologic malignancies, and in patients who have had solid organ transplantation.^{64–67} Although evidence for the use of NIMV in patients with CAP is promising, routine use of this modality in patients without COPD cannot be advocated until further studies have established efficacy and better define ways of identifying which subgroups are most likely to benefit from NIMV.

Immunomodulating agents that may enhance pulmonary host defenses are an exciting area. Ongoing and published research studies using monoclonal antibodies, cytokines, recombinant protein C, and granulocyte colony-stimulating factor have shown variable results.^{56,57} Further studies to determine the benefit of immunomodulators in patients with severe pneumonia and sepsis are warranted.

Summary

Severe CAP is a life-threatening condition that requires ICU admission. Severe CAP is defined by the presence of respiratory failure or symptoms of severe sepsis or septic shock. Around 10% of hospitalized patients present with severe CAP, with a significant mortality rate. Underlying comorbid conditions (most commonly, COPD, alcoholism, chronic heart disease, and diabetes mellitus) are frequently seen in this group of patients. The most common etiologic agents usually found in severe CAP are *S. pneumoniae*, *Legionella* spp., Gram-negative rods (especially *Klebsiella pneumoniae* and *P. aeruginosa*), although half of the cases lack a specific etiologic diagnosis. Early and rapid initiation of empiric antimicrobial treatment should be based on an epidemiologic approach; these factors are critical for a favorable outcome. Initial antimicrobial therapy should consist of an intravenous β -lactam antibiotic plus a macrolide or antipneumococcal fluoroquinolone. Modification of this regimen should be considered in the presence of comorbid conditions and risk factors for specific pathogens. Other nonantimicrobial therapies include mechanical ventilation, vasopressor administration, and continuous monitoring in the ICU.

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