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Optimizing Treatment Outcomes in Severe Community-Acquired Pneumonia

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Abstract

Severe community-acquired pneumonia (CAP) is a life-threatening condition that requires intensive care unit (ICU) admission. Clinical presentation is characterized by the presence of respiratory failure, severe sepsis, or septic shock. Severe CAP accounts for approximately 5–35% of hospital-treated cases of pneumonia with the majority of patients having underlying comorbidities. The most common pathogens associated with this disease are *Streptococcus pneumoniae*, *Legionella* spp., *Haemophilus influenzae*, and Gram-negative enteric rods.

Microbial investigation is probably helpful in the individual case but is likely to be more useful for defining local antimicrobial policies. The early and rapid initiation of empiric antimicrobial treatment is critical for a favorable outcome. It should include intravenous β-lactam along with either a macrolide or a fluoroquinolone. Modifications of this basic regimen should be considered in the presence of distinct comorbid conditions and risk factors for specific pathogens. Other promising nonantimicrobial new therapies are currently being investigated.

The assessment of severity of CAP helps physicians to identify patients who could be managed safely in an ambulatory setting. It may also play a crucial role in decisions about length of hospital stay and time of switching to oral antimicrobial therapy in different groups at risk. The most important adverse prognostic factors include advancing age, male sex, poor health of patient, acute respiratory failure, severe sepsis, septic shock, progressive

radiographic course, bacteremia, signs of disease progression within the first 48–72 hours, and the presence of several different pathogens such as *S. pneumoniae*, *Staphylococcus aureus*, Gram-negative enteric bacilli, or *Pseudomonas aeruginosa*. However, some important topics of severity assessment remain controversial, including the definition of severe CAP. Prediction rules for complications or death from CAP, although far from perfect, should identify the majority of patients with severe CAP and be used to support decision-making by the physician. They may also contribute to the evaluation of processes and outcomes of care for patients with CAP.

Community-acquired pneumonia (CAP) is a common and often serious illness. Between 485 000 and 1 million patients each year are hospitalized in the US for treatment of this condition.[1,2] Along with influenza, pneumonia ranked fifth among the leading causes of death in the elderly in US in 1998.[3] CAP varies widely in the severity of clinical presentation, from rapidly fatal septic shock at one end of the spectrum to almost asymptomatic disease at the other end. Different pathogens, variable virulence among different strains of pathogens, underlying chronic illnesses, and the individual's ability to respond to infection may have an important impact on the presentation and outcome of pneumonia. Severe CAP is now recognized as an entity of its own requiring a distinct clinical approach and antimicrobial therapy. This article focuses on the clinical definition of severe CAP, criteria for intensive care unit (ICU) admission, diagnostic testing, outcome, and prognosis. The most common pathogens associated with this disease and issues related to selecting appropriate antimicrobial therapy are also discussed.

1. Clinical Definition of Severe Community-Acquired Pneumonia (CAP)

Although there is no uniformly accepted definition for severe CAP, many studies have described this entity with reference to patients with respiratory infection admitted to the ICU. This has led to tremendous variability in the patients described by this term, with anywhere between 50–90% of these patients being mechanically ventilated.[4-7]

In 1987, the British Thoracic Society (BTS) attempted, for the first time, to provide a set of working criteria aimed at identifying patients with an increased likelihood of death or complicated course of CAP.[8] The BTS prediction rule was derived from a large prospective study involving 453 inpatients with CAP and was independently validated in 246 inpatients.[9] The BTS rule defines a patient as having a high risk for mortality if at least two of the following features are present: respiratory rate ≥30/minute; blood urea nitrogen >7.0 mmol/L (>19.1 mg/dl); and diastolic blood pressure ≤60mm Hg. According to that study, patients with two or more of these prognostic factors had a 21-fold higher risk of death. An alternative rule including a fourth factor, mental confusion, showed that patients with any two of these four factors had a 36-fold increased risk of a fatal outcome.[10] Although these criteria suggest severe illness, they have not been formally tested to assess the need for ICU admission.

The 1987 American Thoracic Society (ATS) guidelines for CAP suggested that severe illness was characterized by the presence of any one of ten features (table I).[11] Although this definition was based on factors known to be associated with the need

Table I. Criteria for the definition of severe community-acquired pneumonia (CAP) as suggested by the American Thoracic Society[a]

Baseline ('minor') criteria assessed at admission
Respiratory rate >30/min
Severe respiratory failure (PaO_2/FiO_2 <250)
Bilateral involvement in chest radiograph
Involvement of more than two lobes in chest radiograph (multilobar involvement)
Systolic blood pressure <90mm Hg
Diastolic blood pressure <60mm Hg
'Major' criteria assessed at admission or during clinical course
Requirement for mechanical ventilation
Increase in the size of infiltrates by 50% in the presence of no clinical response to treatment or deterioration (progressive infiltrates)
Requirement of vasopressors >4 hours (severe sepsis or septic shock)
Serum-creatinine 2 mg/dl or increase of serum creatinine by 2 mg/dl in a patient with previous renal disease or acute renal failure requiring dialysis (renal failure)

a The presence of at least two of the six 'minor' criteria or one of the four 'major' criteria is necessary for the definition of severe CAP.

PaO_2 = arterial oxygen tension; **FiO_2** = fractional inspired concentration of oxygen.

for intensive care, several studies have subsequently demonstrated that the use of only a single criterion is too liberal, and as many as 45–68% of all patients admitted to the hospital have at least one feature of severe pneumonia.[12,13] Thus, adopting these severity criteria would clearly result in oversensitivity and be a poor predictor of patients at risk of increased mortality. A modified definition achieved more balanced operative indices. Using the modified criteria, the need for ICU admission requires the presence of two of three 'minor' factors including blood pressure ≤90mm Hg, multilobar involvement, arterial oxygen tension/fractional inspired concentration of oxygen (PaO_2/FiO_2) ratio <250 (assessed at admission) or one of two 'major' factors including need for mechanical ventilation or septic shock (present on admission or later during the hospital stay). When the original ATS criteria for severe pneumonia were evaluated, they did not add to the accuracy of predicting the need for intensive care. With the proposed modified definition of severity, the sensitivity of predicting severe disease was 78%, the specificity was 94%, the positive predictive value for increased mortality was 75%, and the negative predictive value was 95%.[12] Therefore, it seems that these five parameters will accurately identify patients with severe CAP. However, the rule is pending a prospective validation in an independent patient cohort, and clinicians should also take into account other potential criteria of severity, such as the presence of mental confusion or pleural effusion. The 2001 ATS guidelines define severe CAP as the presence of at least two of six 'minor' or one of four 'major' criteria in the 1993 ATS statement.[14]

One of the most important weaknesses of severity criteria is that they merge baseline clinical, biological and radiologic variables of outcome with other potentially evolutionary criteria. Consequently, they are not applicable to early hospital or ICU admissions. Because pneumonia is a dynamic process, any assessment of severity takes place at an arbitrary point of disease evolution, and an important minority of patients who do not meet severity criteria on hospital admission may nevertheless be at high risk of developing severe CAP in the following days. We still need a more specific definition that better describes a population needing ICU admission for CAP, as well as predictors of an increased risk for early clinical deterioration toward severe CAP requiring intensive care treatment.

2. Epidemiology

Although data are scarce concerning the frequency of severe CAP, estimates indicate that 5–35%[15] of hospital-treated patients have severe CAP, accounting for 10% of all ICU medical admissions.[16] Approximately four to eight patients per 100 000 individuals per year will require intensive care treatment for CAP, with one-third of the patients having had no previous illness.[17] The most common underlying disease is COPD, which is present in up to half the patients, followed by alcoholism, chronic heart disease and diabetes mellitus.[6,18]

3. Etiology

The organisms most frequently identified among patients with severe CAP are pneumococcus, *Legionella* spp., and *Haemophilus influenzae*, with some series reporting *Staphylococcus aureus* as a common pathogen.[4,7,18-20] Enteric Gram-negative bacteria (especially *Klebsiella pneumoniae*) have been identified at a high frequency in patients with CAP requiring intensive care (around 2- to 3-fold higher) compared with patients admitted to the ordinary hospital ward. Atypical pathogens, such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*, can also lead to severe illness, although they are more frequently considered to be copathogens.[17,20] Viral infections are rare but can be life threatening in elderly and immunocompromised patients.[17,18] They are almost exclusively represented by influenza pneumonia, complicated by direct involvement of the lung parenchyma or by secondary bacterial infection.[21] Mixed infections account for up to 18% of the CAP episodes.[20] Finally, the responsible pathogen is not isolated in around 50% of patients with severe CAP, even when extensive diagnostic testing hs been performed. The failure to identify a pathogen does not seem to be associated with a poorer prognosis.[6,7]

Streptococcus pneumoniae is the most common pathogen isolated in patients with CAP and is present in up to one-third of all patients.[11,12] Four variables have been found to be independently associated with the risk of severe pneumococcal CAP including male sex, nonaspiration pneumonia, septic shock, and no antimicrobial treatment before admission, providing an additional clue to the role of initial empiric antimicrobial treatment in CAP.[22] The emergence of drug-resistant pneumococcus is a worldwide problem. Although the resistance pattern may vary between geographic areas and over time, data from many countries show reduced susceptibility of *S. pneumoniae* to penicillin and other antibacterials in more than 40% of pneumococcal isolates.[20,23] Identified risk factors for the development of drug-resistant strains include age >65 years, alcoholism, noninvasive disease, β-lactam therapy within 3 months of infection, multiple medical comorbidities, exposure to children in a daycare center, and immunosuppressive illness, including therapy with corticosteroids.[14] The effect of age as a risk factor has recently been reported to be less clear.[23] Infection of patients with drug-resistant *S. pneumoniae* has not been associated with increased mortality from CAP

or the requirement for ICU admission, but may be associated with an increased risk of complications.[24-26]

The incidence of legionellosis varies widely depending on the epidemiologic setting and the period under study. Patients with severe community-acquired *Legionella* pneumonia frequently have COPD (41%), and most of them are current smokers (63%).[27] Recent studies from Spain have provided some evidence for a generally decreasing incidence of infection with *Legionella* spp. in patients with severe CAP.[20,28-30] In addition, Woodhead et al.[16] and Hirani and Macfarlane[31] conducted a follow-up study at an ICU and reported only half the number of cases of severe *Legionella* infection reported at the same ICU 10 years earlier (16 vs 30%). A possible explanation for this decreasing incidence of severe legionellosis may be more widespread early use of macrolides, or the so-called 'rise and fall of legionellosis'.

H. influenzae accounts for 6–15% of all cases of severe CAP,[4,6,7,18-20,28] mainly affecting patients with concomitant COPD and elderly patients. The frequency of occurrence of *S. aureus* as a pathogen is also variable, being present in 1–22% of all patients with CAP. Identified risk factors for infection with this organism include recent infection with influenza virus, diabetes, and renal failure.[32] El-Sohl et al.[33] recently looked at 104 patients ≥75 years of age who were admitted to the ICU with the diagnosis of CAP or nursing home-acquired pneumonia. The predominant pathogen in the nursing home group was *S. aureus* (29% vs 7% in the CAP group); in both groups, Enterobacteriaceae were isolated in approximately 15% of patients with pneumonia. The authors also related bacteriology of the severe pneumonia to the functional status of the patients and documented that as the function status declined (activity of daily living score), there was a decrease in the percentage of patients who had pneumococcal infection and an increase in the number of patients who had Gram-negative pathogens and those infected with *S. aureus*. Indeed, risk factors for enteric Gram-negative pathogens include residence in a nursing home, underlying cardiopulmonary disease, multiple medical comorbidities, and recent antibacterial therapy.[14] Infection with *Pseudomonas aeruginosa* accounts for no more than 5% of cases of severe CAP[7,19,20] and should only be considered in patients receiving long-term or prolonged broad-spectrum antibacterial therapy or corticosteroids, as well as in malnourished patients and in patients with bronchiectasis.[14]

Finally, in a large number of patients with severe CAP there is no defined etiological factor, most likely as a result of prior treatment with antibacterials. There is some evidence that *S. pneumoniae* is the most common etiological agent in such episodes of CAP.[34,35]

4. Diagnostic Evaluation

In clinical practice, microbial investigations in patients with CAP have a diagnostic rate of about 15% as a result of which most patients receive an empiric antibacterial regimen.[36] Inappropriate initial antimicrobial therapy is an independent predictor of poor outcome in severe CAP.[3,19] Patients with subsequent changes in their antibiotic therapy, based on culture results, also show significant mortality.[37,38] In order to ensure appropriate initial antimicrobial therapy for patients with CAP, three approaches have been suggested:

- determination of the likely etiology based primarily on clinical presentation ('syndromic approach');
- use of a battery of diagnostic tests to identify a specific etiologic pathogen ('diagnostic approach');
- identification of a limited spectrum of pathogens based on certain host factors and clinical presentation of pneumonia to guide initial antimicrobial management ('empiric approach').

4.1 Syndromic Approach

Classical teaching was that some pathogens, such as *S. aureus*, *H. influenzae*, and Gram-negative enteric bacteria, caused 'typical' clinical syndromes, identical to those produced by *S. pneumoniae*, whereas 'atypical' pneumonias were likely to be caused by *M. pneumoniae*, *Legionella pneumophila* or, more recently, *C. pneumoniae* and viral agents.

Olaechea et al.[30] reported data showing that clinical features can predict microbial etiology in severe CAP and that this information can be used to guide empiric therapy. Using four variables (Acute Physiology and Chronic Health Evaluation [APACHE] II score on admission, serum sodium and phosphorus levels and duration of symptoms), the authors created a score that predicted typical pneumonia with a sensitivity of 90% and specificity of 72%. But, even if this model can be prospectively validated, it will be necessary to define its utility from an outcomes perspective.[39]

Gupta et al.[40] evaluated the syndromic approach for diagnosis in hospitalized patients with CAP and found distinctive features for Legionnaires disease. However, statistical significance is not synonymous with clinical significance, and although the Winthrop-University Hospital (WUH) score discriminated fairly well between patients with *L. pneumophila* pneumonia and those with bacteremic pneumococcal pneumonia, 13–22% of patients with Legionnaires disease were missed by this score. So, as the authors pointed out, the WUH score cannot be used to determine appropriate antibacterial therapy. Since the specificity was low (50–65%), the application of the WUH score could also lead to unnecessary broad coverage. In a separate investigation,

clinical and radiographic features of typical pneumonia were neither sensitive nor specific for the differentiation of pneumococcal and nonpneumococcal etiologies.[29] Moreover, some pathogens have overlap features of both pneumonia syndromes. Therefore, although there are clinical scenarios that may be used to suggest likely etiologic agents, they represent a small minority of severe CAP cases.

4.2 Diagnostic Approach

The diagnostic approach incorporates the use of various diagnostic tests that may help to confirm the presence of CAP and determine an etiology. Identification of the causative agent of CAP should allow narrow-spectrum antibacterial therapy, thereby improving the efficacy of treatment and reducing drug-related toxicity, overall costs and, possibly, the development of antibacterial resistance. Given the much greater risk of adverse outcome in patients with severe CAP, every effort should be made to identify a specific etiology in a timely manner. However, although a large number of diagnostic tests are available, no single test is able to identify all pathogens. In addition, the currently available tests have certain inherent limitations that significantly influence the choice of antibacterial therapy.[4] Finally, evidence that identifying a pathogen improves outcome in patients with severe CAP is also lacking.[6,7]

An etiologic diagnosis may be obtained by noninvasive testing, including blood and pleural fluid cultures, Gram-stain and culture of sputum, serologic testing, and antigen-detection methods for *S. pneumoniae* and *L. pneumophila*. DNA amplification techniques are promising, not only to rapidly screen for pathogens but also for antibacterial resistance. Further refinements in methodology and interpretations of these molecular techniques are nevertheless required. A number of invasive diagnostic procedures to obtain uncontaminated lower airway specimens, including percutaneous fine needle aspiration of the lung and fiberoptic bronchoscopy with a protected specimen brush and/or bronchoalveolar lavage, have reasonable sensitivity and specificity and may also be considered in severely ill patients. However, only a few data are available regarding the diagnostic accuracy of different techniques in severe CAP. In general, standard microbiological tests seems to produce substantially better results in patients with severe illness. This is particularly true for blood cultures reflecting bacteremia, an independent predictor of worse outcome from CAP.[41]

For the patient with severe CAP, diagnostic testing should be performed rapidly, prior to the initiation of antibacterial therapy. Avoid delays in administration of the first dose of an antibacterial. An adverse outcome in an elderly population with CAP has been demonstrated to be a matter of hours of delay from hospital admission to the administration of the first dose of antimicrobials.[42] Except for results from Gram staining of sputum or tracheobronchial aspirates, antigen testing, and intracellular organisms in a Gram stain of bronchoalveolar lavage fluid, no other results are available on the day of diagnostic testing and, therefore, most initial antimicrobial treatment decisions have to be empirical. For these reasons, although diagnostic testing should form part of an optimal approach in the management of the patient with severe pneumonia, the strategy of doing more extensive testing should not form the primary basis on which to make decisions regarding initial antimicrobial treatment of the individual patient. An extensive initial diagnostic workup may be more useful to define local antimicrobial policies based on local epidemiology and resistances.

4.3 Empiric Approach

The initial therapy for severe CAP is of necessity empiric for the aforementioned reasons. The selection of appropriate antibacterial therapy must rely on general microbial patterns based on information easily obtained at the time of initial evaluation. This anticipated empiric antibacterial therapy must evolve based on the changing patterns of isolated organisms and emerging resistance to conventional therapies. Accordingly, correct antimicrobial empirical strategies can only be achieved by prior and periodical epidemiological studies. Moreover, when a very broad- spectrum empiric antibacterial regimen is used, an aggressive diagnostic approach should be done to maximize the possibility of converting to specific therapy as soon as possible. The success of standard empiric regimens in the majority of patients does not justify carelessness in diagnostic efforts for individual high-risk patients.

5. Outcome and Prognostic Factors

Despite improvements in antibacterial therapy, CAP remains one of the most severe infectious diseases. Patients with CAP who require intensive care have been reported to have a mortality rate ranging from 21–58%.[4,31] The reasons for these high ranges of mortality are not entirely clear, and fatality remains unpredictable on clinical grounds alone. The identification of prognostic factors may help clinicians to classify patients with a higher probability of an adverse outcome, define better strategies of prevention and early recognition of severe CAP, and select initial antimicrobial treatment appropriately (table II).

Table II. Outcome and prognostic factors of severe community-acquired pneumonia (CAP)

Risk factors for the acquisition of severe CAP[1,6,17-20,28,43-46]
Age
Chronic obstructive pulmonary disease
Chronic alcohol abuse
Diabetes mellitus
Heart disease
Risk factors for a complicated course of CAP[29,47]a
Age >65 years
Comorbid illness
Temperature >38.3°C
Immunosuppression[b]
High-risk etiologies[c]
Risk factors predicting death from CAP
Premorbid conditions[4,7,8,16,19,22,23,28,45,48,49]
Age
Pre-existing illness
Bedridden patients
Swallowing disorders
Alcoholism
Inadequacy or delay of antimicrobial therapy[d]
Baseline factors (initial evaluation) [5-10,12,16,19,21,27,29,30,33,41,42,45,48,50-56]
High respiratory rate (≥30/min)
Systolic or diastolic hypotension
Mental confusion
Acute Physiology and Chronic Health (APACHE) II score
Simplified Acute Physiology (SAP) score >12–13
Leukopenia
Low lymphocyte count
Increased blood urea nitrogen
Lactate dehydrogenase (≥260 U/L)
Low serum albumin
Multiple lobe radiographic involvement
Microbial etiology[e]
Bacteremia
Disease progression factors[4,6,7,19,22,23,28,33,45,54]
Requirement of mechanical ventilation
Septic shock
Acute renal failure
Ineffective initial antimicrobial treatment
Rapid radiographic spread of pneumonia

a See table III.

b Recent systemic corticosteroid therapy or cancer chemotherapy.

c *Streptococcus pneumoniae*, *Staphylococcus aureus*, enteric Gram-negative bacteria, *Pseudomonas aeruginosa*.

d Prior to hospital admission.

e *S. pneumoniae*, *Enterobacteriaceae*, *S. aureus*, *Klebsiella pneumoniae*, *Legionella* spp., *P. aeruginosa*.

5.1 Risks Factors for Severe CAP

Age is the most common factor known to increase susceptibility to infection of the lower respiratory tract; however, by itself it is not a consideration in the decision not to admit a patient with pneumonia to an ICU. Several studies have observed increases in both the incidence of pneumonia and pneumonia-related mortality with advancing age.[1,43] Lung disease, bronchial asthma and heart disease have been found to be risk factors of pneumonia in the elderly.[44]

As we have previously mentioned, several studies have identified COPD, alcoholism, chronic heart disease, and diabetes as the most common comorbidities associated with severe CAP.[6,17-19,28,45,46] Therefore, these conditions are expected to be potential factors predisposing patients to severe CAP.

In a hospital-based, case-control study, Ruiz et al.[20] found alcoholism (≥80 g/day) to represent an independent risk factor for severe CAP, suggesting that acute effects of alcohol consumption are more important than the total lifetime dose or a history of alcoholism. In this study, there was a trend for treatment with low doses of corticosteroids to be associated with severe CAP, independent of underlying disease. The presence of renal disease as a risk factor for severe CAP also approached significance. In contrast, prior ambulatory antimicrobial treatment was protective against severe CAP.

5.2 Risks Factors for a Complicated Course of CAP

Simple clinical and radiological data have been shown to be useful in severity and risk assessment of ambulatory patients with pneumonia.[57] However, a limited but a significant proportion of patients initially thought to have mild pneumonia will require hospitalization during the course of the disease. In one study,[47] five variables were found to predict clinical deterioration of patients initially treated on an ambulatory basis. These variables included age >65 years, comorbid illness, temperature >38.3ºC, immunosuppression (recent systemic corticosteroid therapy or cancer chemotherapy), and the presence of high-risk etiologies (*S. aureus*, enteric Gram-negative bacteria, aspiration or post-obstructive pneumonia). The risk of treatment failure increased linearly with the number of risk factors present, and the authors suggested considering patients for hospitalization when more than one of these variables were present. In another study,[29] pneumonia requiring admission to the ICU was independently associated with pathogens such as *S. pneumoniae*, Gram-negative enteric bacilli, and *P. aeruginosa*. A clear limitation of these studies is that pathogens causing pneumonia are seldom known at the initial evaluation and, therefore, cannot form part of the initial risk assessment.[58]

Table III. Risk factors for a complicated course of community-acquired pneumonia (including death) according to the American Thoracic Society (ATS) guidelines[14]

Age >65 years
Coexisting illness
Chronic obstructive lung disease
Bronchiectasis
Malignancy
Diabetes mellitus
Chronic renal failure
Congestive heart failure
Chronic liver disease
Chronic alcohol abuse
Malnutrition
Cerebrovascular disease
Postsplenectomy
Hospital admission within the previous year
Physical findings
Respiratory rate ≥30 breaths/min
Diastolic blood pressure ≤60mm Hg or systolic blood pressure <90mm Hg
Pulse ≥125/min
Fever <35 or ≥40°C
Confusion or decreased level of consciousness
Evidence of extrapulmonary sites of infection
Laboratory findings
White blood cell count $<4 \times 10^9$/L or $>30 \times 10^9$/L or neutrophil count $<1 \times 10^9$/L
PaO_2 <60mm Hg or $PaCO_2$ >50mm Hg while breathing room air
Serum creatinine >1.2 mg/dl or BUN >20 mg/dl (>7 mmol)
Hematocrit <30% or hemoglobin <9 mg/dl
Arterial pH <7.35
Evidence of sepsis or organ dysfunction: metabolic acidosis or coagulopathy
Radiographic findings
Multilobar involvement
Cavities
Pleural effusion
Rapid radiographic spreading[a]

a Usually cannot be determined at the time of admission.

BUN = blood urea nitrogen; **PaO_2** = arterial oxygen tension; **$PaCO_2$** = arterial carbon dioxide tension.

The ATS guidelines[14] have outlined a variety of risk factors that increase the likelihood of a complicated course (including death) for CAP in hospitalized patients treated with antibacterials. These risk factors for an adverse outcome are listed in table III. In a multicenter retrospective analysis, patients with CAP admitted to hospital had a mean of five risk factors present, and a variety of clinical outcome variables including admission to the ICU; mean hospital stay and mortality were linearly correlated with the number of risk factors present.[13]

5.3 Risk Factors Predicting Death from CAP

More than 40 prognostic factors have been identified to be associated with death from CAP in multivariate analysis.[58] A meta-analysis comprising more than 33 000 patients from 127 study cohorts found ten independent predictors of death, including male sex, diabetes, neurologic disease, neoplasia, hypotension, tachypnea, hypothermia, leukopenia, multilobar infiltrates, and bacteremia. The presence of pleuritic chest pain was a protective factor.[41] These results may be biased by including studies from different periods, populations and settings, so the repeated identification of prognostic factors in different studies is an important additional issue. From a clinical point of view, the prognostic factors of hospital-treated CAP can be classified as basic, baseline, and disease progression factors.[59]

5.3.1 Basic Factors

These factors represent the premorbid condition of the patient and refer to general epidemiological characteristics as well as the history of the episode of pneumonia prior to hospitalization. Among the basic prognostic factors for a fatal outcome, the most frequently reported are age[4,6,8,16,22,28,45] and pre-existing illness,[4,19] although it should be kept in mind that about half of the patients who die do not have any apparent debilitating disease and that fatalities do also occur in a significant number of younger patients. A multivariate analysis on risk and prognostic factors of CAP demonstrated that if patients were bedridden or had prior swallowing disorders, they had a 7- to 10-fold higher risk of death, making these two variables key descriptors of comorbidity in patients. In this study, age by itself was not a significant factor related to prognosis.[48] In another study, alcoholism was associated with not only a more severe clinical presentation of CAP but also increased the risk of fatal outcome by 5-fold.[49] In contrast, in other studies, comorbidities did not seem to influence outcome.[22,45]

Several authors have confirmed the adverse prognostic implications of inadequate antimicrobial therapy or delay in appropriate therapy prior to hospital admission.[7,8,19,22,33] Thus, not only adequacy but also immediacy of antimicrobial treatment determines the outcome of CAP, probably because the early reduction of the bacterial load is critical in order to limit the potentially harmful inflammatory response to the pathogen. Later on, the inflammatory cascade may evolve beyond the point of recovery and run relatively independently of the causative organism and, therefore, of antimicrobial therapy.[60,61]

Nuorti et al.[62] found that cigarette smoking was the strongest independent risk factor for invasive pneumococcal disease. Additional host factors that influence the outcome of infection are just beginning to be understood. These include the observation that 50% of patients with bacteremic pneumococcal pneumonia were homozygous for the human Fc gamma receptor (FcγR)IIa-R131 allotype, which binds weakly to immunoglobulin (Ig) G in comparison with 29% of uninfected control individuals.[50] Waterer et al.[63] have also found a significant association between the LTα+250 (TNFβ+250) AA genotype and the risk of septic shock in patients with CAP. It seems, therefore, that a tendency to particular presentations of CAP may also be genetically determined.

5.3.2 Baseline Factors

These factors include all data available at the initial evaluation or within the first 24 hours after admission and reflect acute pneumonia-related illness. Of the baseline factors, the most closely associated with poor prognosis are vital-sign abnormalities such as a high respiratory rate (≥30/minute),[8-10,12,41,48] systolic or diastolic hypotension,[6,8-10,12,41,51] mental confusion,[6,8-10] APACHE II score on admission,[28,52] and a simplified acute physiology score (SAPS) >12[42] or >13.[6] Significant laboratory factors are leukopenia,[8,21] low lymphocyte count,[51,53] increased blood urea nitrogen,[8-10,12] lactate dehydrogenase (≥260 U/L),[51] and low serum albumin.[8,50] Multiple lobe radiographic involvement is an additional risk factor for a fatal outcome.[12,33,41,45,48,54]

The independent impact of different microbial agents is another important prognostic issue. There are several pathogens that have been repeatedly reported to be associated with death in multivariate analysis. These agents include *S. pneumoniae*,[6,51] and *Enterobacteriaceae*.[6] *S. aureus*,[16,55] *K. pneumoniae*,[5,56] *Legionella* spp.,[27] and *P. aeruginosa*[19,45] have also been recognized as pathogens commonly seen in patients with severe CAP and have been reported to have a prognostic bearing. In contrast, another study showed that microbial etiology was not linked to prognosis.[64]

Several studies on severe pneumococcal CAP have reported mortality rates of 21–35%.[22,65,66] Shock and a very low serum albumin level (<26 g/L) were the only clinical features that differentiated survivors from nonsurvivors in one of the studies[65] whereas, in another study [22] a multivariate analysis showed that leukopenia <3 500/mm^3, age over 65 years, septic shock, sepsis-related complications, ICU complications, and inadequate antimicrobial therapy worsened the prognosis of severe pneumococcal CAP.

A recent study of severe CAP caused by *Legionella* [27] reported a mortality rate of 31%, and independent factors related to poor outcome were hyponatremia ≤136 mEq/L, APACHE II score >15, and lack of improvement of pneumonia within 48 hours of admission. Inappropriate specific treatment for *L. pneumophila* was related to poor outcome in the univariate analysis.

A rapidly fatal clinical course with mortality rates of 64% have been reported in staphylococcal pneumonia[16] and bacteremic *K. pneumoniae* pneumonia in alcoholics.[56] The mortality of severe CAP caused by *P. aeruginosa* reached 100% in one series;[19] considering that the standard treatment for severe CAP does not cover *P. aeruginosa* adequately, this high rate could have been a result of inadequate initial antibacterial therapy. Accordingly, it is important to identify specific risk factors for these high-risk microorganisms to optimize the initial therapeutic approach in severe CAP.

Regardless of the causal pathogen involved, bacteremia has been consistently found to be an important prognostic factor,[6,7,19,29,30] although at least one study has not found pneumococcal bacteremia to be associated with an increased mortality.[65]

5.3.3 Disease Progression Factors

These evolutionary factors reflect a patient's apparent deterioration, particularly within the first 48 hours after initiation of antimicrobial treatment and during the course of intensive care treatment. These parameters are not as useful for initial treatment decisions as basic and baseline factors, but they may be helpful in managing patients with severe CAP.[59] The requirement of mechanical ventilation represents an adverse prognostic factor reflecting disease progression, with reported mortality rates >50%.[4,6,19,45,54] Some specific parameters, such as the use of positive end-expiratory pressure or the need for an inspiratory oxygen fraction of >0.6, have been found to be associated with adverse prognostic potential.[19] The disease progression factors most frequently identified in different studies are septic shock,[6,7,19,28,33,45,54] acute renal failure,[28] ineffective initial antimicrobial treatment[7,19,22,33] (because the infecting pathogens are either resistant, not responsive, or not covered by the initial antibacterial regimen, or because of superinfections of the lung), and rapid radiographic spread of pneumonia within 48 hours despite adequate treatment with antimicrobials.[19,28] Unfortunately, most of these prognostic factors do not help in changing or adjusting medical attitudes aimed at a decrease of mortality due to severe CAP.

5.4 Prognostic Scoring Systems

Multiple studies have used multivariate statistical models in an attempt to create prognostic rules for outcome in CAP. These could be helpful in clinical decision making. Fine et al.[67] elaborated a prognostic index for patients with CAP that included six

predictors including age >65 years, pleuritic chest pain, vital sign abnormality, altered mental status, high-risk etiology, and neoplastic disease. The authors assigned a different score to each of these factors according to their coefficients in a multivariate mortality model. The rule was simple and accurately classified low-risk patients, however, the inclusion of etiologic information precluded its use at the initial evaluation of the patients. In a subsequent study,[68] the same authors developed a pneumonia-specific severity of illness (PSI) score derived from 20 items that comprised three demographic variables, five comorbidity features, five physical examination findings, and seven factors from laboratory/imaging data. For each variable present, points are added to the score and patients are then placed into five risk classes. Patients in risk classes I–III are at low risk (<1%) of mortality and can be managed as outpatients, whereas for those patients with risk classification IV or V the mortality rates were 9 and 27%, respectively; patients in classes IV and V risk classification should be admitted to hospital. Fine et al.'s prediction rule was not specifically designed as an admission guideline and consequently did not evaluate the need for ICU admission. Nevertheless, patients in class V are more likely to require intensive care treatment. Fine et al.'s prediction rule has been proven to accurately predict length of stay, intensive care requirement, and the risk of death due to pneumonia in an elderly European population.[69]

The potential of the scoring system attributed to Fine et al. has been explored in other studies.[70,71] Marrie et al.[72] conducted a randomized evaluation of a critical pathway for the management of CAP among 19 Canadian teaching and community hospitals. The antibiotic levofloxacin was administered to patients in the intervention arm, whereas antimicrobial therapy for patients in the conventional arm was left to the discretion of the attending physician. The PSI score was utilized for decisions related to site of care. At intervention hospitals, the admission rate was lower for low risk patients (classes I–III) than it was for conventional management (31 vs 49%, $p = 0.013$); there were no differences in the rates of complications, readmission, or mortality between patient groups. However, patients with CAP at low risk of death may experience unexpected deterioration and, hence, should be clinically re-examined within the first 24–72 hours after the initiation of empiric antimicrobial treatment. In hospitalized patients, the median time for overall clinical stability is 3 days, and it is clearly correlated to initial severity. Once stability is achieved, clinical deterioration requiring ICU treatment occurs in <1% of cases.[73]

Since the first report of the BTS guidelines on CAP, several studies have confirmed excellent operative characteristics of the original[9] or slightly modified prognostic rules,[10] with sensitivities ranging from 70–90%, and specificities ranging from 76–84%.[58] Two studies however, failed to confirm the favorable prediction results of these prognostic rules.[69,74] Generally, the predictive power of the BTS rules is high, as these rules are focused on identifying high-risk patients by including variables that reflect the most important prognostic factors (e.g. acute respiratory failure by tachypnea, septic shock by measurement of blood urea nitrogen levels, mental confusion, hypotension, and tachycardia).

Leroy et al.[64] developed and prospectively validated a prognostic score for severe CAP. This score, based on 16 predictors of mortality, performed well in classifying patients as having low or high risk of death during ICU stay. One of the limitations of this risk index is that it merges basic and baseline variables with other factors assessed only during the evolution of CAP. As a consequence, this score is not applicable in assessing prognosis at the time of ICU admission. In a subsequent study,[54] these authors identified six independent predictors of ICU mortality including age ≥40 years, anticipated death within 5 years, non-aspiration pneumonia, chest radiograph involving more than one lobe, acute respiratory failure requiring mechanical ventilation, and septic shock. These predictors were used to classify patients into three risk classes. For patients in low- (I) and high-risk classes (III), the initial prediction of final outcome appeared correct. For patients in class II (imprecise initial prognosis), three evolutionary factors were essential to accurately predict outcome; hospital-acquired lower respiratory tract superinfections, nonspecific CAP-related complications, and sepsis-related complications. After validation, this simplified rule may have important therapeutic or preventive implications.

Pascual et al.[75] have derived a prediction rule to quantitate the risk of hospital mortality in patients with CAP requiring mechanical ventilation using data obtained during the first 24 hours of assisted ventilation. Among the predictor variables, the degree of lung injury measured by the hypoxemia index was the most important prognostic factor. The model showed good discriminative ability (88% accuracy in outcome classification) with better prediction performance than SAPS and APACHE II in patients with CAP and respiratory failure. In this study, survivors had a significantly shorter duration of hospital stay prior to mechanical ventilation than nonsurvivors, suggesting that the timing of intubation may have a great impact on prognosis.[76]

In general, prediction rules may oversimplify the way physicians interpret predictor variables and neglect the importance of patient preferences. In addition, although, mortality prediction rules may be of importance in helping physicians identify patients who need hospitalization or ICU admission, they cannot replace physicians' clinical judgment in the decision making process.[14] Whatever the real therapeutic interest of such indices for the over-

all population of patients with CAP, the implications for the medical care of patients with severe CAP requiring intensive care treatment appear questionable.

6. Treatment

An early and aggressive approach is crucial in decreasing mortality among severely ill patients with CAP. Patients with severe CAP are admitted to the ICU for supportive antimicrobial and nonantimicrobial therapies.

6.1 Antimicrobial Therapy

Among the factors associated with an increased mortality for CAP, the most amenable to medical intervention is the administration of appropriate antibacterials. The initial therapy for CAP is mostly empiric, and the choice of antibacterial agents is often guided by consensus guidelines.[14,77,78] These recommendations for the empirical treatment of CAP focus on covering the possible associated etiological agents according to published findings from different groups of patients. Physicians must be aware of the local microbial and susceptibility patterns in the etiology of CAP and the risk factors for pathogens likely to be resistant to standard empiric antimicrobial regimens. Various guidelines for the initial selection of antimicrobial regimens for treating patients with severe CAP[14,77,79] are shown in table IV.

The pathogens most frequently identified among patients with severe CAP include *S. pneumoniae*, *H. influenzae*, *Legionella* species (and other atypicals), and aerobic Gram-negative bacilli. Accordingly, the most common empiric antibacterial regimen suggested includes a third generation cephalosporin that would be active against drug-resistant pneumococcus in combination with an advanced generation macrolide or a fluoroquinolone.

In a retrospective study in 213 hospitalized patients, Burgess and Lewis[80] concluded that the addition of a macrolide to a nonpseudomonal third generation cephalosporin as initial empiric therapy for the treatment of CAP may not be necessary. Nevertheless, Gleason et al.[81] showed that in almost 13 000 elderly inpatients with CAP initial therapy with a second generation cephalosporin plus a macrolide, a nonpseudomonal third generation cephalosporin plus a macrolide, or a fluoroquinolone alone was independently associated with a lower 30-day mortality rate than was therapy with a nonpseudomonal third generation cephalosporin alone in patients with PSI IV and V. The implications from these findings have been that routine therapy against atypical pathogens may be important even in elderly patients with CAP. This study, however, is not without its flaws: retrospective design; lack of information about the reasons for giving a specific patient a certain therapy; and discrepancies between the outcome of different groups receiving dual therapy (i.e. individuals who received a β-lactam/β-lactamase inhibitor combination plus a macrolide had an increased mortality rate for reasons that have not been adequately explained).

In another population-based retrospective study, the inclusion of a macrolide or a fluoroquinolone in the initial empiric treatment of CAP was also associated with improved survival, but this association varied from year to year, probably as a result of a temporal variation in the incidence of pneumonia caused by atypical pathogens.[82] The role of quinolone monotherapy in severe CAP due to pneumococci is currently uncertain and, in this setting, quinolones should be used as combination therapy (usually with a β-lactam) and used only as a replacement for macrolide antibacterials.[14,77-79]

In the past few years, an increasing prevalence of *S. pneumoniae* with reduced susceptibility to fluoroquinolones has been reported from many countries, although resistance rates still remain low in general.[83-86] A recent study shows that presence of COPD (odds ratio [OR] 10.3), nosocomial origin of the bacteria (OR 16.2), residence in a nursing home (OR 7.4), and exposure to a fluoroquinolone during the 12 months prior to admission (OR 10.7) are factors independently associated with levofloxacin-resistant *S. pneumoniae* colonization or infection.[87] The use of fluoroquinolones should be restricted in these patients.

Patients with risk factors for *P. aeruginosa* should receive combination therapy (two antipseudomonal agents) and provide coverage for drug-resistant pneumococcus and *Legionella*. This could be achieved with fourth generation cephalosporins, such as cefepime and cefpirome, or other selected β-lactam (piperacillin/tazobactam, imipenem, meropenem) plus an aminoglycoside (preferably tobramycin or amikacin) and either azithromycin or a new quinolone. Alternatively, a selected β-lactam in combination with ciprofloxacin is a reasonable choice in this setting.[14,77,78] Antipseudomonal agents such as cefepime, piperacillin/tazobactam, imipenem, and meropenem are not recommended for routine use and should be reserved for patients with risk factors for *P. aeruginosa* infection.

Other modifications of the basic antimicrobial regimen should also be considered in the presence of risk factors for distinct pathogens. Hence, in bedridden patients favoring aspiration, especially with neurological disease, anaerobes and *S. aureus* should be covered. This latter organism should also be considered, as well as Gram-negative enteric bacilli, in elderly patients admitted from nursing homes. In the presence of antimicrobial pretreatment for >48 hours, again Enterobacteriaceae have to be taken into account. Finally, a significant percentage of patients with severe CAP are infected with pathogens not covered by the

usual empiric antibacterial regimens, thereby supporting an aggressive diagnostic approach in patients with severe CAP.[88,89]

In patients with CAP where the causative pathogen can be identified, directed therapy should be used. However, it should be taken into account that single effective drug therapy of severe bacteremic pneumococcal pneumonia can be associated with a higher risk of death compared with dual therapy.[90]

All treatments should initially be administered intravenously. Criteria for switching from intravenous to oral antibiotics include a functioning gastrointestinal tract and the ability to tolerate antibiotics by mouth, the subjective diminishment of cough and shortness of breath, normal temperature readings for previously febrile patients, stable blood pressure, and a white blood cell count returning toward normal.[14,91,92] The optimal duration of antimicrobial therapy for CAP has not been defined in prospective studies. The presence of underlying diseases, the severity of illness at the onset of treatment, and the subsequent hospital course should be considered in determining the duration of antibacterial therapy. Generally, severe CAP can be treated for 7–10 days, although longer periods should be preferred in patients treated long term with corticosteroids or in case of pneumonia due to *P. aeruginosa* or atypical pathogens, such as *Legionella* spp.

It has been estimated that approximately 10% of patients with CAP may experience progressive life-threatening pneumonia.[29] If the patient's clinical condition is not improving or is deteriorating after initial empiric therapy, the causative organism may not be covered by the initial antibacterial regimen. Alternatively, the infection could be caused by an unusual organism, or the patient may have suppurative complications of pneumonia. Finally, a noninfectious illness that can mimic pneumonia should be considered. Arancibia et al.[93] found that treatment failures in hospitalized patients with CAP were mainly infectious in origin and included unusual pathogens, persistent pathogens (mostly due to microbial resistance to the administered initial antimicrobial therapy), and nosocomial infections. These nosocomial infections were particularly frequent in patients with progressive pneumonia and were the only cause of treatment failure independently associated with death. These data support repeated microbial investigation in all patients with antimicrobial treatment failures in order to detect possible nosocomial pneumonia, which would require a therapeutic approach involving the administration of specific secondary antimicrobials.

6.2 Nonantimicrobial Treatment

Despite effective antimicrobial therapy, a significant percentage of hospitalized patients with CAP die within the first 3–4 days. In fact, mortality rates have remained virtually unchanged in the last few decades. Management guidelines for severe CAP have been widely adopted, but there has been no reduction in mortality. Although patients today are probably older than 20 years ago and have severe comorbid diseases more often, it is also likely that factors other than early diagnosis, use of appropriate antibacterials, and prompt ICU transfer may influence the outcome of severe CAP.[31] Currently, the most promising approaches in the field of nonantimicrobial treatment include mechanical ven-

Table IV. Preferred and alternative empirical selection of antimicrobial regimens for treating patients with severe community-acquired pneumonia according to different guidelines

Organization	Preferred	Alternative or special considerations
ATS	IV β-lactam (cefotaxime, ceftriaxone) + IV macrolide (azithromycin) or IV fluoroquinolone	IV antipseudomonal β-lactam (cefepime, imipenem, meropenem, piperacillin/tazobactam)[a] + IV aminoglycoside, + IV macrolide (azithromycin) or intravenous nonpseudomonal fluoroquinolone
IDSA	Extended spectrum cephalosporin (cefotaxime, ceftriaxone) or β-lactam/β-lactamase inhibitor + antipneumococcal fluoroquinolone or macrolide	Antipseudomonal agents[b] + fluoroquinolone (including high-dose ciprofloxacin)
		Antipneumococcal fluoroquinolone[c] ± clindamycin
		Antipneumococcal fluoroquinolone[d] ± clindamycin or metronidazole or β-lactam/β-lactamase inhibitor
BTS	IV broad spectrum β-lactamase stable antibiotic (amoxicillin/clavulanic acid, cefuroxime, cefotaxime, ceftriaxone) + macrolide ± rifampicin (rifampin)	Antipneumococcal fluoroquinolone + benzylpenicillin

a Risks for *Pseudomonas aeruginosa*.

b Structural lung disease.

c β-lactam allergy.

d Suspected aspiration.

ATS = American Thoracic Society; **BTS** = British Thoracic Society; **IDSA** = Infectious Diseases Society of America; **IV** = intravenous.

tilation (invasive and noninvasive), treatment of hypoxemia, and use of immunomodulators.

6.2.1 Mechanical Ventilation

A significant number of patients with severe CAP develop respiratory failure and often require mechanical ventilation with the main objectives of improving hypoxemia and preventing the development of adult respiratory distress syndrome. Noninvasive mechanical ventilation (NIMV) refers to the delivery of assisted mechanical ventilation without endotracheal intubation, thereby preserving airway defense mechanisms, reducing the incidence of ventilator-associated pneumonia, and improving patient comfort, with a shorter stay in the ICU and hospital.[94-97] NIMV efficacy seems to be related more to the presence of underlying COPD than to the cause that precipitates acute respiratory failure.[95] Although evidence for the use of NIMV in patients with severe CAP is promising, there are only limited data on its efficacy in these high-risk patients. Further research is still required to determine to what extent endotracheal intubation can be avoided by this noninvasive approach, which subgroups of patients are more likely to benefit from NIMV, and whether it effectively improves the outcome of patients with pneumonia and respiratory failure.

6.2.2 Treatment of Hypoxemia

Patients with pneumonia and hypoxemic acute respiratory failure may have intrapulmonary shunting and low ventilation-perfusion units reaching 50% of cardiac output. Additionally, dead space may rise up to 60% of alveolar ventilation, and mean pulmonary artery pressure may also be moderately incremented.

In unilateral pneumonia, positioning the unaffected lung down may increase PaO_2 by an average of 10–15mm Hg by improving blood flow to well ventilated areas.[98] Anti-inflammatory drugs that act as cyclo-oxygenase inhibitors may potentially reverse partial ablation of hypoxic pulmonary vasoconstriction caused by metabolites of arachidonic acid.[99,100] However, the role of these drugs remains doubtful,[101,102] and a recent study has shown that while leading to a modest improvement in intrapulmonary shunt, aspirin (acetylsalicylic acid) does not induce significant changes in arterial oxygenation.[102] The effects of prostacyclin on gas exchange and hemodynamics have also been investigated in ventilated patients because of severe CAP. Low doses of aerosolized prostacyclin significantly decreased the mean pulmonary artery pressure and intrapulmonary shunt without simultaneous changes in systemic arterial pressure or cardiac output, thus improving PaO_2 by a mean of about 20mm Hg.[103] Inhaling small amounts of nitric oxide also causes selective vasolilation of ventilated lung regions, thereby reducing pulmonary hypertension and improving gas exchange without producing systemic vasodilation.[104] In a preliminary study of patients with severe pneumonia, nitric oxide inhalation increased PaO_2 by a mean of about 20mm Hg.[105] Both aerosolized prostacyclin and nitric oxide deserve further randomized, blinded trials to determine their impact on treatment outcome.

6.2.3 Immunomodulators

In pulmonary infections, cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, and IL-8 secreted by the activated alveolar macrophages are able to attract polymorphonuclear leukocytes (PMN) into the alveoli from the vascular compartment; the PMNs phagocytose the invading pathogens. However, excessive cytokine production has deleterious effects, with a systemic inflammatory response that can lead to multi-organ failure and death. Additionally, it has been suggested that the quantification of some of these cytokines may have prognostic implications.[106] The modulation of the inflammatory response, which aims to establish a balance between the beneficial and harmful effects, has received considerable interest.[107]

Immunomodulating agents may modify pulmonary host defenses by enhancing the intrapulmonary influx of PMNs as well as having bactericidal activity against bacterial pathogens. Levels of granulocyte colony stimulating factor (G-CSF), one of the cytokines that acts on neutrophil proliferation, maturation, and function, significantly increase during bacterial pneumonia. This finding suggests that G-CSF may have a key role in the regulation of host defense response against invading pathogens. A recent multicenter, randomized study has evaluated the safety of filgrastim (recombinant methionyl human G-CSF) administration in 18 immunocompetent ventilated patients with severe pneumonia.[108] This pilot study suggests that filgrastim is well tolerated when administered to patients with severe pneumonia at dosages of 300 μg/day and appears to improve bacterial clearance. Its use as adjuvant therapy for severe pneumonia is worth exploring.

Activated protein C, an endogenous protein that promotes fibrinolysis and inhibits thrombosis and inflammation, is another important modulator of coagulation and inflammation associated with severe sepsis. Treatment with drotrecogin alfa (recombinant human activated protein C) has been reported to significantly reduce mortality in patients with severe sepsis (24.7 vs 30.8%), although the incidence of serious bleeding among treated patients was higher than in the placebo group.[109]

The impact of glucocorticoids on outcome in pneumonia is unknown. Marik et al.[110] investigated the effects of a single bolus of hydrocortisone on the clinical course of patients with severe CAP. They randomized patients to receive either 10 mg/kg of hydrocortisone or placebo prior to starting antibacterial therapy and found that hydrocortisone had no effect on the serum

TNFα levels or the clinical course of patients with severe CAP. In another study,[111] however, the mortality rate in patients with pneumonia receiving corticosteroids was 36% compared with 67% in patients not receiving corticosteroids. Moreover, survivors receiving glucocorticoids had lower serum TNFα levels in comparison with nonsurvivors, suggesting that glucocorticoids decrease systemic and lung inflammatory responses in patients with severe pneumonia receiving concomitant antimicrobial therapy.[111] Corticosteroids also appear to be of value in the treatment of patients with life-threatening varicella pneumonia. In a nonrandomized study on clinical improvement of patients with severe varicella pneumonia, Mer and Richards[112] observed that those patients who received corticosteroids in addition to antiviral therapy had no mortality and significantly shorter ICU and hospital stays, and there was a trend towards the development of fewer complications. Future prospective, controlled, randomized trials should assess whether glucocorticoids have any favorable clinical effect in patients with severe pneumonia. The therapeutic goal in severe pneumonia, in the near future, will probably be to determine the threshold at which inflammation is beneficial but not deleterious.

7. Conclusions

Severe CAP requiring admission to an ICU is associated with a high mortality rate. The assessment of severity is one of the most important issues in the management of patients with CAP. Age, comorbid illness and vital sign abnormalities have been reported to be the main criteria of determining severity of pneumonia. Several studies involving patients with CAP have developed severity prediction rules to determine the site of care and the need for intensive care treatment. Further studies are needed to validate current predictive rules in different settings and define variables reflecting initial severity as well as a state of increased risk for early deterioration. The most common etiologic agents found in severe CAP are pneumococcus, *Legionella*, and *H. influenzae*, with some series reporting an increasing frequency of enteric Gram-negative bacteria. Accordingly, combination therapy with a β-lactam and macrolide or fluoroquinolone is the most frequently suggested empiric antimicrobial regimen. Promising nonantimicrobial approaches are currently under study.

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