Review Article

Severe community-acquired pneumonia: Severity and management

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ABSTRACT

Community-acquired pneumonia (CAP) is a leading cause of morbidity and mortality worldwide. "Severe CAP" (sCAP) identifies a group of patients who have severe disease and require Intensive Care Unit admission. Recommendations for antibiotic treatment for sCAP are based on illness severity, frequency of specific pathogens and local microbial resistance patterns. The challenges to patient management include the emergence of the high prevalence of multidrug-resistant in CAP, mainly from institutionalizing patients. A new approach is the evaluation of biomarkers as C-reactive protein, procalcitonin on the diagnosis, prognosis and therapy duration of sCAP with promising results. Implementation of guidelines for CAP treatment should be emphasized in order to increase survival. The benefits of steroid use in patients with severe pneumonia have not been proven yet by current literature.

Key words: Intensive Care Unit, multidrug-resistant pathogens, prognostic scores, severe community-acquired pneumonia, therapy

INTRODUCTION

Community-acquired pneumonia (CAP) represents a public health problem of substantial magnitude, with an annual incidence ranging 1.6-10.6/1000 adult population in Europe. The incidence of CAP increases importantly with age, having a wide spectrum of clinical severity from a self-limiting disease to septic shock and acute respiratory distress syndrome.

The term "severe CAP" (sCAP) identifies a group of patients who have severe disease, who require Intensive Care Unit (ICU) admission, are prone to have complications and poor outcomes, and who require a higher level of care.[1,2] The incidence of sCAP increases the last decade. Particularly, in a study of Woodhead *et al*.,[3] they identified a 128% increase in admissions for CAP from 12.8/unit to 29.2/unit during the study period compared to a 24% rise in total ICU admissions ($P < 0.001$).

The main aim of this review is to analyze what is currently the best therapeutic approach to sCAP.

SEVERITY OF PNEUMONIA

Many studies of the epidemiology of patients with CAP have demonstrated the importance of assessing severity of illness and stratifying patients on the basis of their risk of mortality. The pneumonia severity index (PSI) and CURB-65,[4] are the most popular prediction rules, do not have sufficient operating characteristics to be useful for making ICU triage decisions in sCAP. On 2007, the Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) issued guidelines[1] on the management of CAP include specific criteria to identify patients for ICU admission. This rule recommended that the presence of one of the major or three or more of the nine minor criteria would indicate ICU admission [Table 1].

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Other models specific to sCAP have been developed, including a recent Australian model called SMART-COP,[5] a Spanish model called CURXO.[6]

None of the rules have been prospectively demonstrated to avoid late transfers or lower mortality. Delayed ICU admission was associated with two-to 2.6-fold increased risk for hospital mortality in two recent studies compared with direct admission from the emergency room.[7,8] In an interesting study published in 2009, Renaud *et al*.[8] proposed a mixed French-American score called the Risk of Early Admission-ICU index. In patients without obvious reason for immediate admission to the ICU from the emergency they identified 11 baseline characteristics to be predictors for ICU admission between 1st and 3rd day from ward.

The role of biomarkers in the inflammatory response and their correlation to the severity of the infection continues to be a subject of growing interest. Ramírez *et al*.[9,10] assessed the prediction for ICU admission of biomarkers and the IDSA/ATS guidelines minor criteria for s CAP and suggest that the patients with s CAP by minor criteria and low levels of procalcitonin (PCT) may be safely admitted to wards.

ETIOLOGY

The spectrum of causal pathogens in severe pneumonia is broader than that in nonsevere cases. *Streptococcus pneumoniae* is still the leading pathogen, followed by *Haemophilus influenzae*, *Staphylococcus aureus*, *Legionella pneumophila*, *Enterobacteriaceae*, especially *Escherichia coli* and *Klebsiella* species, and *Pseudomonas aeruginosa*.[11] Bacteremia is more common than CAP and up to 20% of sCAP episodes are caused by polymicrobial infection. Aspiration pneumonia is a common cause of sCAP and is generally polymicrobial with Gram-negative and Gram-positive anaerobes. In another study of Cilloniz *et al*.,[12] including 3523 patients with CAP, in those admitted in the ICU the most common etiologies were *S. pneumoniae* (42%), mixed etiologies (22%) and atypical pathogens (18%). *S. pneumoniae* had the highest number of deaths, although the relative mortality rates were higher for *S. aureus*, Gram-negative enteric bacilli, *P aeruginosa* and mixed etiologies.

Table 1: Criteria for ICU admission

Major criteria
Invasive mechanical ventilation
Septic shock with the need for vasopressors
Minor criteria
Respiratory rate ≥30 breaths/min
$PaO_2/FiO_2 \leq 250$
Multilobar infiltrates
Confusion-disorientation
Uremia (BUN level ≥20 mg/dL)
Leucopenia (WBC count <4×10^9/L)
Thrombocytopenia (platelet count <100×10^9/L)
Hypothermia (core temperature <36°C)
Hypotension (SBP <90 mmHg) requiring aggressive fluid resuscitation

ICU: Intensive Care Unit, BUN: Blood urea nitrogen, WBC: White blood cell, SBP: Systolic blood pressure

MULTIDRUG-RESISTANT ORGANISMS IN SEVERE COMMUNITY-ACQUIRED PNEUMONIA

Multidrug-resistant organisms (MDROs) that cause CAP, represent an emerging problem, because of the increasing number of residents living in healthcare facilities and the appearance of community acquired methicillin resistant *S. aureus* community-associated methicillin-resistant *S. aureus* (CA-MRSA). In an attempt to evaluate risk factors for acquiring MDR bacteria in CAP, Aliberti *et al*.[13] found that hospitalization in the preceding 90 days (odds ratio [OR]: 4.87, 95% confidence interval [CI]: [1.90-12.4]; $P < 0.001$) and residency in a nursing home (OR, 3.55,95% CI, [1.12-11.24]; $P < 0.031$) were independent predictors for an actual infection with a resistant pathogen.

Shorr *et al*.,[14] discovered a simple risk score that appears valid for assessing the probability of an MDRO in patients initially hospitalized with CAP. Its parameters were as follows: Recent hospitalization, living in a long-term care facility, chronic hemodialysis and ICU admission within 24 h of evaluation in the ED, with an area under the receiver operating characteristic (AU ROC) for the risk score 0.71 whereas the AU ROC for healthcare-associated pneumonia equaled 0.62. Further studies are needed for evaluation of these scores and identification the patients with MDR CAP.

THERAPY

Treatment for sCAP remains largely empirical. Identifying the infecting pathogens is very difficult because it is frequently difficult to collect lung samples for microbiological evaluation and because of the lack of rapidly available diagnostic tests that allow the differentiation of viral and bacterial etiologies in most cases.

The goal of appropriate antimicrobial treatment, therefore, is to maximally reduce or eradicate the bacterial load in order to achieve clinical success and minimize the potential for development of resistance. Specific risk factors (e.g., chronic obstructive pulmonary disease [COPD], bronchiectasis) should be taken into account on an individual basis.

In patients with CAP and septic shock, delay must not be >1 h after diagnosis.[1,15] In a multicenter study of Kumar *et al*.,[16] included 2154 septic shock patients, showed that effective antimicrobial administration within the 1st h of documented hypotension was associated with increased survival to hospital discharge.

The most consistent data comes from studies of sCAP, where guideline adherence is associated with reduced mortality.[17,18]

In the study of Bodí *et al*.,[17] included 529 patients with sCAP, significantly higher mortality was documented among patients with nonadherence to guidelines treatment (33.2% vs. 24.2%).

- According to the guidelines for the management of CAP in Europe, and US,[1,2] the therapy depends on the presence of the risk factors for *P. aeruginosa* infection. These are chronic or prolonged use of broad-spectrum antibiotic therapy, the presence of structural lung diseases (bronchiectasis), repeated exacerbations of COPD, corticosteroid therapy, malnutrition, human immunodeficiency virus, and other forms of immunosuppression[1,2] [Table 2].

a. For patients without pseudomonal risk an intravenous β-lactam plus either a macrolide or a respiratory fluoroquinolone is recommended.
b. In patients with risk factors for pseudomonal infection, an antipseudomonal β-lactam should be combined with either levofloxacin or ciprofloxacin or the antipseudomonal β-lactam can be combined with both an aminoglycoside and either azithromycin or a respiratory quinolone [Table 2].

When CA-MRSA is suspected (prior influenza-like illness, necrotizing severe pneumonia), vancomycin or linezolid should be added to the other recommended agents.

Anaerobic coverage with the combination of a cephalosporin with clindamycin is indicated only in patients with a risk for aspiration, such as alcoholism, loss of consciousness and neurological disease and dysphagia due to mechanical or neurological upper digestive tract dysfunction.

Macrolide combination therapy was associated with lower mortality compared with a quinolone combination, a consistent finding in almost all large databases of patients with sCAP.[19-22] Rodríguez *et al*., in CAPUCI study,[19] found that in the subset of ICU patients who had CAP and shock, combination antibiotic therapy improved survival rates (OR = 1.69; *P* = 0,01), suggesting that combination therapy may be beneficial in more severe cases. Another observational study of patients with sCAP found that patients with CAP and shock who were treated with combination antibiotic therapy (58% with a third-generation cephalosporin plus a macrolide), compared to those treated with monotherapy (42% fluoroquinolone), had a higher 28-day in-ICU survival (hazard ratio 2.69, 95% CI: 1.09-2.60).[20] Survival was not different between combination therapy and monotherapy in ICU patients without shock. The benefit of a macrolide may also explain the finding of greater clinical relapse in patients randomized to a b-lactam alone if their streptococcal urinary antigen was positive.[22]

From several studies has become increasingly clear that the benefit of combination therapy in sCAP is seen only when a macrolide is part of the regimen, especially in pneumococcal bacteremia.[23,24]

The guidelines recommend antibiotic therapy for 7-10 days.[15] Longer treatments suggesting to slow response, non-drainable focci, *S. aureus* bacteremia, some fungal or viral infections and immunological deficiencies (neutropenia). The SCC guidelines now include the use of biomarkers, especially PCT, to assist in decisions regarding discontinuation of empiric antibiotics and when considering the diagnosis of candidiasis. The largest randomized trial published to date reported that a PCT guided strategy to treat suspected bacterial infections in nonsurgical patients could reduce antibiotic exposure.[25]

Table 2: Therapy of CAP admitted to ICU

No risk factors for *Pseudomonas aeruginosa*
Non-antipseudomonal cephalosporin III+macrolide
Or
Moxifloxacin or levofloxacin±antipseudomonal cephalosporin III
Risk factors for *Pseudomonas aeruginosa**
Antipseudomonal cephalosporin[a] or acylureidopenicillin/b-lactamase inhibitor or carbapenem (meropenem preferred up to 6 g possible, 3×2 in 3 h infusion+ciprofloxacin[b] or+macrolide+aminoglycoside (gentamycin, tobramycin, amikacin)

*Include: (1) Recent hospitalization [A3], (2) Frequent (>4 courses/year) or recent administration of antibiotics (last 3 months) [A3], (3) Severe disease (FEV1 <30%) [A3], (4) Oral steroid use (>10 mg of prednisolone daily in the last 2 weeks) [A3]. [a]Ceftazidime+penicillin G coverage for *Streptococcus pneumoniae*, [b]Levofloxacin 750 mg/24 h or 500 mg twice a day is an alternative, FEV1: Forced expiratory volume in 1 s, CAP: Community-acquired pneumonia, ICU: Intensive Care Unit

ADJUNCTIVE THERAPIES

The corticosteroids can be used in patients with sCAP because of:

1. Are the most powerful inhibitors of inflammation and
2. In patients with s CAP and septic shock, a relatively insufficient adrenal response has been observed during infection, associated with a higher risk of death.[26]

The relationship between low-dose corticosteroid use and mortality in patients with sCAP remains unclear. In a recent study from Japan including 6925 patients with sCAP in the ICU, they concluded that low-dose corticosteroid use may be associated with reduced 28-day mortality in patients with septic shock complicating CAP.[27] Snijders *et al*.[28] published a randomized controlled trial of 213 CAP patients; in which 104 received prednisolone 40 mg once daily (orally or intravenously) for 7 days. The subgroup analyses of patients with severe pneumonia (54 with CURB-65 >2, 93 with PSI Classes IV-V) did not show significant differences in clinical outcome.

Two meta-analysis on this subject, one of Nie *et al*.[29] from China, and the other of Confalonieri *et al*.,[30] suggested that only in sCAP a prolonged corticosteroids therapy result in a beneficial effect on mortality.

Several studies indicate that noninvasive ventilation (NIV) may also work in patients with sCAP, particularly in patients with COPD.[1] In a study of Ferrer *et al*., from 3 hospitals in Spain, comparing with oxygen therapy, NIV decreased the need for intubation (13% vs. 29%, $P = 0.010$), the incidence of septic shock (6% vs. 17%, $P = 0.028$), and the ICU mortality (9 vs. 21 $P = 0.028$) and increased the cumulative 90-day survival ($P = 0.025$), in patients with severe respiratory failure.[31]

CONCLUSION

When managing patients with CAP, it is important to choose the most appropriate site of care and the appropriate empiric antimicrobials. Implementation of guidelines for CAP treatment should be emphasized in order to increase survival. Based on the antiinflammatory properties of macrolides their role for combination therapy in patients with sCAP waits to be established. Similarly, some reports have demonstrated a favorable impact of glucocorticosteroid treatment on the prognosis of sCAP, but ongoing investigations of anti-inflammatory molecules probably represent the key point of severe infection management in the near future.

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