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Managing CAP in the ICU

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Abstract Despite remarkable progress in diagnosis and antibiotic therapy, mortality due to pneumonia has not changed significantly and ICU admissions are increasing. The management includes early evaluation of severity, collection of microbiological cultures, and appropriate antibiotic administration. The prognostic scores as the ATS/IDSA rule, the PIRO, or SCAP system are valuable in timely recognition of critically ill patients with community-acquired pneumonia (CAP) requiring admission to ICU. Implementation of guidelines for CAP treatment should be emphasized in order to increase survival. Guidelines for antibiotic management for severe CAP are based on illness severity, covering most likely bacterial and atypical pathogens and the level of ICU antibiotic resistance. Combination therapy suggested in patients with nonrefractory septic shock and severe sepsis pneumococcal bacteremia also. Recent studies suggest that steroid therapy may be valuable in nonrefractory septic shock from sCAP.

Keywords ICU · Community-acquired pneumonia · Septic shock · Treatment

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Introduction

Generally, the population of severe community-acquired pneumonia (sCAP) represents 10 % of patients hospitalized with CAP, with an incidence that increases in recent years. Particularly, in a study of Woodhead et al. [1], an 128 % increase in admissions for CAP from 12.8/unit to 29.2/unit during the 9-year study period compared to a 24 % rise in total ICU admissions ($p<0.001$) was reported. After ICU admission, mortality is elevated reaching up to 30–40 % and the length of hospital stay is prolonged, often with complications and chronic rehabilitation is needed.

CAP is a complex and evolving inflammatory disease, and critical deterioration could be present with respiratory failure, circulatory insufficiency, aggravation of comorbidities, or hospital-acquired illnesses.

sCAP is a progressive disease, and in the event of evolution from a local to a systemic infection, the following spectrum of sepsis-related complications may develop: sepsis, severe sepsis, septic shock, and multiple-organ dysfunction [2]. CAP is the most common cause of sepsis and septic shock worldwide. In the USA, CAP is responsible for 1.2 out of 2.05 million (59 %) yearly hospital admissions for sepsis [3]. In a interesting study including 1339 patients hospitalized for CAP in the USA and Canada, Dremsizov and colleagues [4] reported that severe sepsis developed early in 48 % of the 639 hospitalized CAP patients while 4.5 % (61 patients) of them presenting with septic shock. Additionally, delayed ICU transfer for respiratory arrest or shock is associated with 2–2.6-fold increased risk for hospital mortality compared with direct admission from the emergency department (ED) [5, 6••, 7••].

The main aim of this review is to describe the optimal treatment of patients with sCAP admitted in the ICU, in order to improving patient outcomes.

Severity Assessment: Prognostic Scores

The identification of patients with severe pneumonia requiring ICU admission is vital. The admission of a patient with CAP to the ICU is a serious and individualized decision, depending on the hospital facilities, ICU availability, disease severity, and the patient's medical history.

Multiple scoring systems have been developed to help recognize patients with CAP at risk for ICU admission from ED. The IDSA/ATS guidelines of 2007 for the management of CAP defined a prediction rule consisting of one of two major criteria or three or more of the nine minor criteria (Table 1) that would indicate ICU admission [8]. The two major criteria of the IDSA/ATS rule refer to patients with acute respiratory failure requiring invasive mechanical ventilation (MV) or septic shock.

A new generation of scores (SCAP rule, SMART-COP, and REA-ICU), specifically developed to predict sCAP, focuses on the severity of the pneumonia on presentation rather than on age and underline diseases. The main characteristic of these scores is their high negative predictive value, in all the studies, suggesting that these scores could be more applicable for the exclusion of sCAP than categorizing pneumonia patients into severity classes.

In Australia, Charles and colleagues [9] developed the SMART-COP, a relatively simple eight-point-based severity tool to predict which patients will require intensive respiratory or vasopressor support (IRVS) during hospitalization.

A mixed French-American score called the REA-ICU index [6••] identified 11 baseline characteristics to be predictors for early ICU admission between first and third day from ED or ward. The REA-ICU index stratified patients into four risk classes with an ICU admission rate on days 1 to 3 ranging from 0.7 to 31 %.

Other investigators developed a severity assessment tool to predict mortality in CAP based on the predisposition, insult, response, organ dysfunction (PIRO) and had a better performance than APACHE II and ATS/IDSA criteria in patients with sCAP [10, 11].

There is a growing interest in the use of new biomarkers as procalcitonin [12], endothelin-1 [13], co-peptin [14], proatrial natriuretic peptide [15, 16], or adrenomedullin [17] to improve the diagnosis and stratification of CAP, combined with severity scores in some studies.

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 <4×109/L)
Thrombocytopenia (platelet count <100×109/L)
Hypothermia (core temperature <36 °C)
vHypotension (SBP <90 mmHg) requiring aggressive fluid resuscitation

Source: [5]

ICU intensive care unit, PaO_2/FiO_2 ratio of arterial partial pressure of oxygen (PaO_2) to fraction of inspired oxygen (FiO_2), *BUN* blood urea nitrogen, *WBC* white blood cell, *SBP* systolic blood pressure

Microbiology

Streptococcus pneumoniae is the main pathogen that causes CAP worldwide, independent of age and severity [8]. Other pathogens associated with sCAP include the gram(−)s *Haemophilus influenza*, *Klebsiella pneumoniae*, from the atypicals the *Legionella* spp., *Staphylococcus aureus* and respiratory viruses. In a study of Choi et al., using PCR testing, about one third of patients with sCAP had viral infections, 9.1 % (18 of 198) of patients had bacterial-viral coinfection, but there was no difference in mortality between the two groups of patients [18]. Recently, Cilloniz and colleagues, including 362 patients, reported that polymicrobial infection was common in sCAP (11 % of patients) with respiratory viruses diagnosed in 15(39 %) of cases of polymicrobial pneumonia [19]. Mixed infections with atypical pathogens count for 5–40 % of cases, according to studies, and should be covered in the initial antimicrobial regimen.

P. aeruginosa is a frequent gram(−) pathogen in sCAP with specific risk factors, especially in those with severe COPD with frequent hospitalizations, bronchiectasis, cystic fibrosis, those taking antibiotics for a long time(>10 mg for >1 month) and immunosuppressed patients (HIV, corticosteroid therapy, malnutrition) [20].

Multidrug-resistant pathogens (MDRs) that cause sCAP represent an emerging problem, because of the increasing number of residents living in health care facilities and the appearance of community-acquired methicillin-resistant *S. aureus* (CA-MRSA). Asian studies show high frequency of MDR pathogens in CAP [21], especially in elderly who received antibiotics recently or have comorbidities. In a cohort of patients presenting to the hospital with CAP complicated by respiratory failure, Schreiber et al. [22] diagnosed resistant pathogens in 33 % of the study population.

In attempts to evaluate risk factors for acquiring MDR bacteria in CAP, Aliberti et al. [23] and Shorr et al. [24••] discovered simple risk scores representing an improvement over an

HCAP-based approach. Further studies are needed for validation of these scores and early identification of patients with MDR CAP.

Treatment

In order to achieve a more uniform approach toward empirical treatment of CAP, guidelines for the management of CAP have been developed in many countries and by different scientific committees in the past 20 years. The guidelines focused on the significance of timely, appropriate and aggressive management of patients presented with sCAP [8].

The two most fatal complications of CAP in the first month are respiratory failure and multiple organ dysfunction syndrome. A subanalysis of PORT was reported within 90 days after hospitalization for CAP; only half of the deaths are related to acute illness, and other factors as underlying diseases as dementia, immunosuppression, and active cancer may influence mortality [25].

Both common sense physiologic interpretation and several studies have recommended that delay in appropriate therapy with broad spectrum antibiotics is related with increased mortality in sepsis due to CAP [26]. In patients with CAP progressing to septic shock, delay must not be >1 h after diagnosis [1, 25]. In a multicenter study including 2154 septic shock patients, Kumar et al. [27] demonstrated that initiation of appropriate antibiotic therapy into the first hour of documented hypotension was associated with increased hospital survival.

Initial Resuscitation

The initial measures includes blood cultures before antibiotics, fluid resuscitation with 30 mL/kg/body weight to target a mean arterial blood pressure (MAP) of at least 65 mmHg, central venous pressure (CVP) of 8–12 mmHg, and a central venous oxygen saturation (ScvO2)<70 % within 6 h of diagnosis.

Resuscitation requires the use of intravenous fluids and vasopressors, oxygen therapy and MV provided as necessary.

Aggressive fluid resuscitation is considered the most crucial part of all the major interventions forming the Surviving Sepsis Campaign (SSC) bundles. The recommended choice is the colloids or crystalloids—in fluid challenge aliquots of 1000 mL of crystalloid or 300–500 mL—to reach a minimum of 30 ml/kg of crystalloids and not the hydroyethyl starch (HES) [2]. Furthermore, the use of albumin-containing solutions for the resuscitation of patients with sepsis was associated with lower mortality compared with other fluid resuscitation regimens, in a meta-analysis published in 2011 [28].

Another suggestion of resuscitation is the addition of resolution of lactate elevation or lactate clearance—especially during the first 6 h—to the SSC resuscitation bundles [29].

One of the benefits of aggressive fluid therapy is a 15 % reduction in vasopressor use during the first 6 h. This early reduction in vasopressor therapy further reduces the need for controversial therapies such as vasopressin and corticosteroid therapy (Table 2).

When aggressive fluid administration cannot provide an adequate MAP, vasopressors should be promptly initiated, as the longer that hypotension goes on, the lower the survival rate. The SSC [2] suggests to start with norepinephrine and add epinephrine or vasopressin (0.03 U/min) when is needed to restore MAP>70 mmHg. Dopamine should be used only in patients with absolute or relative bradycardia.

This is followed by early hemodynamic optimization of DO_2 guided by preload (fluid administration guided by CVP), afterload (vasopressor use based on MAP), arterial oxygen content (CaO_2), blood transfusion for low central $ScvO_2$ and contractility (augmentation by inotropes for a persistently low SvO_2) [2].

General Supportive Care

Recommendations for (a) blood transfusion if hemoglobin is <7 g/dL in the absence of tissue hypoperfusion, ischemic coronary artery disease, or acute hemorrhage and (b) blood

Table 2 Initial resuscitation

Begin goal-directed resuscitation during first 6 h after recognition
• Begin initial fluid resuscitation with crystalloid and consider the addition of albumin
• Consider the addition of albumin when substantial amounts of crystalloid are required to maintain adequate arterial pressure
• Avoid hetastarch formulations
• Begin initial fluid challenge in patients with tissue hypoperfusion and suspected hypovolemia, to achieve ≥30 mL of crystalloids per kilogram of body weight†
• Continue fluid-challenge technique as long as there is hemodynamic improvement
• Use norepinephrine as the first-choice vasopressor to maintain a mean arterial pressure of ≥65 mmHg
• Use epinephrine when an additional agent is needed to maintain adequate blood pressure
• Add vasopressin (at a dose of 0.03 units/min) with weaning of norepinephrine, if tolerated
• Avoid the use of dopamine except in carefully selected patients (e.g., patients with a low risk of arrhythmias and either known marked left ventricular systolic dysfunction or low heart rate)
• Infuse dobutamine or add it to vasopressor therapy in the presence of myocardial dysfunction (e.g., elevated cardiac filling pressures or low cardiac output) or ongoing hypoperfusion despite adequate intravascular volume and mean arterial pressure

Source: [2]

† The guidelines recommend completing the initial fluid resuscitation within 3 hours

glucose management, to obtain blood glucose ≤180 mg/dL [30].

Ventilation: Invansive (MV) or Noninvansive (NIV)

The delivery of oxygen is paramount and begins with either supplemental oxygen, or noninvasive or invasive positive pressure mechanical ventilation (PPMV).

The indications are severe hypoxia, hypercapnia, severe metabolic acidosis, altered mental status, and a persistently low $ScvO_2$.

During mechanical ventilation, the use of a lung protective-ventilation strategy (with low VT 6–8 ml/kg PBW and plateau pressure goal % 30 cm H_2O) in patients who have ALI/ARDS, including those who have sCAP is recommended [5].

The benefits of noninvasive ventilation (NIV) in ARF of patients with sCAP have been demonstrated with different degrees of evidence in several studies.

In one of the first studies, Confalonieri et al. report that in patients with sCAP and ARF (refractory hypoxemia and/or hypercapnia with acidosis), NIV was found useful to significantly decrease endotracheal intubation rate and length of ICU stay and mortality in the subgroup of COPD patients [31]. Later, in a study from three hospitals in Spain, including 105 patients with hypoxemic ARF, Ferrer et al. confirmed the benefits of NIV in avoiding intubation (OR 0.20; p=0.003), and improving 90-day survival (p=0.025), in patients with severe respiratory failure [32].

Antibiotic Therapy

Antimicrobial treatment for sCAP remains largely empirical, targeting the most likely pathogens.

Before the initiation of antibiotics, at least two samples of blood cultures should be obtained, one intravenous and the other from a vascular catheter.

According to the guidelines for the management of sCAP in Europe and USA [8, 20], patients should be stratified CAP according to the presence of risk factors for *P. aeruginosa* infection (Table 2).

- For patients without pseudomonal risk an intravenous β-lactam plus either a macrolide or a respiratory fluoroquinolone is recommended.
- If pseudomonal infection is a consideration, 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.
- 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 oropharyngeal dysphagia due to neurological disease.

Combination Antibiotic Therapy

The controversy regarding combination antibiotic therapy in patients with sCAP is coming from the lack of randomized controlled trials (RCT) comparing combination therapy versus monotherapy in patients with sCAP in the ICU [5].

Initially, Waterer et al. [33] reported in a study of 225 patients with severe bacteremic pneumococcal pneumonia that mortality was threefold greater when a regimen of single effective therapy was used than in a regimen of dual effective therapy. A recently published RCT [34], consisting of 580 adults with moderately sCAP, did not find noninferiority of β-lactam monotherapy compared to β-lactam and a macrolide regimen regarding outcomes (mortality, complications, length of stay, recurrence of pneumonia).

From several studies, it has become increasingly clear that the advantage of dual antibiotic therapy in sCAP is seen mainly when a macrolide is part of the combination, especially in pneumococcal bacteremia [35•]. This effect is presumed to be secondary to the immunomodulatory effect rather than the antimicrobial effects of macrolides.

A multicenter study from Europe which include 270 patients with sCAP and shock confirmed that patients who were treated with a third-generation cephalosporin plus a macrolide compared to those treated with FQ had a higher 28-day in-ICU survival (hazard ratio [HR]=2.69, 95 % CI 1.09–2.60) [36••]. But, combination therapy did not increased survival in patients without shock. In addition, Martin Loeches et al., in a prospective observational study of 208 patients with sCAP from 27 ICUs, showed that combination therapy with macrolides associated with lower ICU mortality in intubated patients [37••].

The guidelines recommend antibiotic therapy for 7–10 days. Longer treatments suggesting to slow response, nondrainable focci, *S. aureus* bacteremia, some fungal or viral infections and immunological deficiencies (neutropenia).

The recent SCC guidelines correlate the levels of biomarkers, especially procalcitonin (PCT), with the duration of antibiotic treatment (de-escalation or stop treatment) and when considering the diagnosis of candidiasis.

After the first 6 h of resuscitation, we must think of four points: (i) fluid resuscitation must be continued; (ii) further or additional vassopressors, as dobutamine, epinephrine, or vasopressin; (iii) adjunctive therapies, as corticoids; and (iv) re-evaluation of antibiotic choices.

When the causative pathogen has been identified, de-escalation should be performed by selecting the most effective and safe antibiotic against the causative pathogen.

GCs and the Inflammatory Response

Despite decades of experimental animal and human trials, the role of corticosteroid therapy in sCAP remains uncertain and controversial, more vague than in septic shock.

Firstly, a pilot study by Monton et al. [38], including intubated patients with sCAP, suggested that treatment with GCs decrease systemic and lung inflammatory responses in mechanically ventilated patients with severe pneumonia. On the contrary, a large multicentric RCT published in 2008, involving 499 patients with septic shock, concluded that hydrocortisone at a physiological dose does not decrease mortality, even if the drug hastens reversal of shock [39••].

Prospective, randomized trials referring to GCs in sCAP are the Confalonieri et al. [40] in 2005, Sabry and Omar [41] and Fernandez-Serrano et al. [42] in 2011, and Torres et al. [43••] in 2015.

The results of the last RCT of Torres et al. [43••] support that the addition of low dosages of GCs in the initial antibiotic empiric regimen can diminish inflammatory response and reduce the risk of treatment failure in patients with sCAP.

Meduri et al. [44] in a RCT with 91 patients with early ARDS due to sCAP showed that patients treated with prolonged methylprednisolone infusion (1 mg/kg/day) had a higher rate of extubation (p=0.07) and significant reduction in C-reactive protein levels(p=0.06) by day 7. GC treatment reduce the duration of MV (p=0.13) and ICU mortality (p= 0.3) but not significantly.

These trials that investigated steroid treatment for sCAP for at least 5 days showed improvement in oxygenation (PO2/ FiO2); however, only the trial by Confalonieri et al. found a mortality benefit.

The value of GCs seems to have been proven in bacterial meningitis and pneumonia caused by *Pneumocystis jiroveci*.

For patients with sCAP, risk assessment should take into consideration patients with severe chronic obstructive pulmonary disease and asthma that may have received intermittent treatment with steroids before their septic episode, and, therefore, have iatrogenic adrenal insufficiency, needing steroid replacement [8].

Recent guideline for sepsis recommended that corticosteroids are not to be used for treating septic shock, unless the patients' endocrine function is not intact or that patients have corticosteroid history [28].

Conclusion

When managing patients with CAP, implementation of guidelines for CAP treatment should be emphasized in order to increase survival. In sCAP, scientific evidence is limited until now.

The use of appropriate initial broad antimicrobial therapy, the combination treatment in septic patients, the de-escalation when causative pathogen has been identified and the efficacy of using steroids in the nonrefractory septic patient have lead to considerable advance in pneumonia's outcomes.

Compliance with ethical standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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