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# Corticosteroids as Adjunctive Therapy in Severe Community-Acquired Pneumonia

C. Cillóniz, A. San José, and A. Torres

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## Introduction

Mortality in community acquired pneumonia (CAP) has not decreased in the intensive care unit (ICU), despite progress in antimicrobial therapy [1, 2]. Approximately 10% of patients hospitalized with CAP are admitted to the ICU [3]. In a multicenter study by Mongardon et al. in patients with severe pneumococcal CAP admitted to the ICU, the mortality rate was 29%, with high proportions of patients in septic shock and needing mechanical ventilation [4]. Severe CAP is a progressive disease and patients may die despite early and adequate antibiotic treatment. The host local and systemic inflammatory immune response in patients with severe CAP is exacerbated and disproportionate and this is probably the main cause for the high mortality in this specific population, as it contributes to impaired alveolar gas exchange, sepsis and end-organ dysfunction [5]. In this specific population of patients with severe CAP, adjuvant treatments, such as corticosteroids, may be beneficial.

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C. Cillóniz · A. San José · A. Torres (✉)

Department of Pneumology, Institut Clinic del Tórax, Hospital Clinic  
Barcelona, Spain

Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona  
(UB)

Barcelona, Spain

Ciber de Enfermedades Respiratorias (Ciberes)

[www.ciberes.org](http://www.ciberes.org)

email: [atorres@clinic.ub.es](mailto:atorres@clinic.ub.es)

## Systemic Adjunctive Corticosteroid Therapy in Severe CAP

The principle action of corticosteroids is the inhibition of the expression and action of several cytokines involved in the immune inflammatory response to pneumonia [6]. It is known that, in CAP patients, the use of systemic adjunctive corticosteroid therapy attenuates the local and systemic inflammatory response [7], and may potentially reduce the development of acute respiratory distress syndrome (ARDS), sepsis and mortality. Sibila et al. [8], in a study of *Pseudomonas aeruginosa* pneumonia in mechanically ventilated piglets, observed a lower lung bacterial burden and less severe histological pneumonia in piglets treated with corticosteroids plus antibiotics compared to antibiotics alone.

Several randomized controlled trials (RCT) have been performed in humans, the majority of which included hospitalized patients with non-severe CAP. The results of these trials have been negative [9], or have demonstrated a reduction in length of stay [10] or time to clinical stability [11]. To date, four studies have been performed in patients with severe CAP [12–15]. A meta-analysis published by Nie et al. [16] showed that in a subgroup of patients with severe CAP, steroids reduced mortality. More recently, a meta-analysis [17] showed that the use of systemic corticosteroids in CAP was associated with a moderate reduction in the need for mechanical ventilation, development of ARDS and, with high certainty, a reduction in time to clinical stability and duration of hospitalization. This study also showed a possible reduction in mortality, but this effect was seen mainly in the subgroup of patients with severe pneumonia.

However, most of these RCTs had important limitations: a) the inclusion of many patients with low severity without ICU admission, which makes it difficult to demonstrate differences in clinical outcomes, such as treatment failure and mortality, because of the rates of these outcomes; and b) the inclusion of patients regardless of the initial level of inflammation. To date, this latter variable has not been taken into account in the any of the RCTs. CAP patients with a marked inflammatory response have high levels of C-reactive protein (CRP), higher rates of treatment failure [18] and worse mortality rates [19]. Furthermore, there are marked differences in variables in the majority of RCTs, regardless of dosages, type and length of steroid treatment, which makes it very difficult to compare results. The primary end-points are different between studies, and some of them, such as length of stay or even time to clinical stability, are ‘soft’ endpoints: length of stay depends on other variables and clinical stability is driven by the persistence of fever which is, in fact, down-regulated by corticosteroids.

More recently, Torres et al. [20] performed an RCT comparing methylprednisolone (0.5 mg/kg every 12 h for 5 days) vs. placebo, with important specific characteristics: a) the authors included only patients with severe CAP with major or minor modified criteria of the American Thoracic Society, or with a Pneumonia Severity Index (PSI) risk class V; b) they chose patients with a large systemic inflammatory response, with a threshold for serum levels of CRP of 15 mg/dl; c) treatment failure was defined as early (clinical deterioration indicated by the

development of shock, need for invasive mechanical ventilation, not present at baseline, or death, within 72 h) or late (radiographic progression or persistence of respiratory failure, development of shock, need for invasive mechanical ventilation not present at baseline, or death, between 72 and 120 h after treatment initiation), and was the primary end-point, rather than mortality. In addition, it is known that treatment failure in CAP is associated with higher mortality, as previously shown in the study by Menendez et al. [21].

The principal results showed a decrease in the treatment failure rate from 31 to 13% ( $p=0.02$ ). Corticosteroids reduced the risk of treatment failure with an odds ratio of 0.34. Mortality did not differ significantly between groups, but the study was not designed to find differences in mortality (10% in the methylprednisolone arm vs. 15% in the placebo arm,  $p=0.37$ ). The reduction in treatment failure was more evident in late treatment failure (3% vs. 25%,  $p=0.001$ ), and especially in radiographic progression, which was one of the variables included in the composite definition of late treatment failure (2% vs. 15%,  $p=0.007$ ). The rates of adverse effects were small and similar between arms. A limitation of this study was the long recruitment period (8 years) and the use of methylprednisolone for 5 days only, with an abrupt interruption of the treatment.

The results of this study, which found fewer treatment failures, particularly late treatment failure, and less radiographic progression, may be explained by stopping of the progression to ARDS or a potential blocking of the Jarisch-Herxheimer reaction, which is thought to be due to high concentrations of cytokines released after the initiation of antibiotics, possibly through the release of endotoxins or other bacterial mediators in patients with a high bacterial burden, as occurs in meningococcal disease [22].

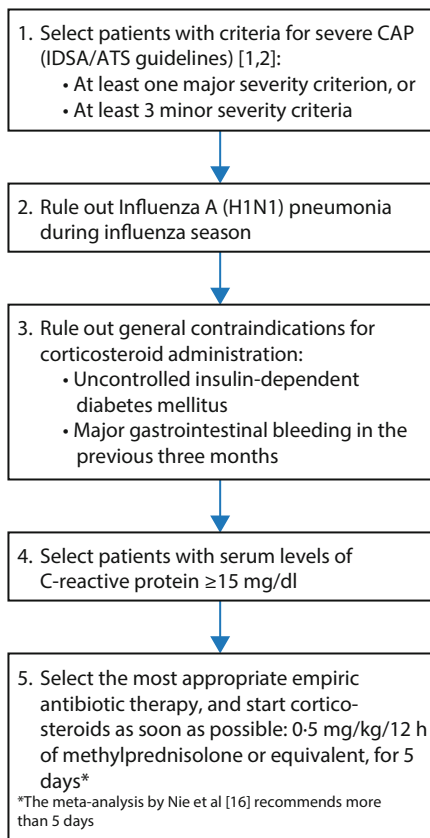
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## Corticosteroids in Patients with Severe CAP with Marked Inflammation and Non-Influenza Pneumonia

In patients with severe CAP, treatment with corticosteroids should be considered in clinical practice. It is important to select patients with severe CAP with a marked inflammatory response measured by CRP. Another important point is to exclude patients with influenza pneumonia, as growing evidence suggests that corticosteroids increase mortality in patients with influenza pneumonia [23]. Little information is available on the possible effect of corticosteroids on other viral pneumonias caused by adenovirus, rhinovirus, respiratory syncytial virus, or others. However, high serum levels of CRP indicate that pure viral pneumonia is unlikely. We propose an algorithm for the administration of corticosteroids as an adjunctive treatment for CAP (Fig. 1).

There is another CAP population in which corticosteroids may have a role to play. Shindo et al. [24] described the risk factors for 30-day mortality in patients with pneumonia who received appropriate initial antibiotics. They found that blood levels of albumin,  $\text{pH} < 7.35$ , respiratory rate  $> 30$  breaths per minute, and blood urea nitrogen of at least 7.14 mmol/l were independent risk factors for mortality. In

**Fig. 1** Proposed algorithm for administration of corticosteroids in severe community-acquired pneumonia (CAP)



the accompanying editorial [25], it was pointed out that these results would make it possible to develop a predictive score for use in clinical trials of immunomodulatory drugs. This indication needs new RCTs.

Future studies should include the following research steps:

- (a) Investigation of the potential synergies between macrolides and corticosteroids. Such investigations can be performed in animal models of pneumonia. An animal study of *Mycoplasma pneumoniae* pneumonia [26] showed histological benefits of combined clarithromycin and dexamethasone treatment compared to either treatment alone.
- (b) A meta-analysis, using individual data with a particular focus on severe CAP, which can provide useful clinical information.
- (c) Randomized trials in other CAP populations, such as patients with a high risk of mortality despite appropriate antibiotics.

## Conclusion

Mortality rates in severe CAP remain high [27, 28]. Corticosteroids are the most effective and widely used anti-inflammatory drugs. Corticosteroids are useful in patients with severe CAP with a high degree of systemic inflammatory response and in whom influenza pneumonia has been ruled out, and can help to decrease treatment failure and probably mortality in these patients.

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