Editorial

Severe community-acquired pneumonia: Corticosteroids as adjunctive treatment to antibiotics

Severe community-acquired pneumonia (SCAP) represents up to 18% of the hospitalized patients with CAP, and is a major cause of admission to the Intensive Care Unit (ICU), also is associated with high morbidity and mortality.[1,2]

In a multicenter study carry out in French about severe pneumococcal CAP admitted to ICU, the overall mortality rate was 29% although antibiotherapy was adequate in 92% of the cases, septic shock (77%) and needing mechanical ventilation (84%) also was present in high proportion on this patients.[3]

SCAP is a progressive disease; patients might die despite an early and adequate antibiotic treatment. This is probably due, in part, to a misbalanced and disproportionate local and systemic inflammatory response that contributes to impairment of gas exchange, severe sepsis, and multiple organ dysfunctions.[4]

Systemic adjunctive corticosteroid therapy attenuates the local and systemic inflammatory response,[5] they inhibit expression of proinflammatory cytokines and accelerate expression of anti-inflammatory cytokines.[5] Downregulation of systemic inflammatory response in SCAP patients may improve the clinical course, and may potentially decrease the development of acute respiratory distress syndrome (ARDS), sepsis, and mortality in this population.

In an experimental model of *Pseudomonas aeruginosa* pneumonia in mechanically ventilated piglets, we observed a lower lung bacterial burden and less severe histological pneumonia in piglets treated with corticosteroids plus antibiotics.[6]

In humans, several trials have been performed mostly in hospitalized patients with non-SCAP. The meta-analysis of Nie *et al*.[7] showed that the use of corticosteroids was associated with improved mortality in severe CAP but not in the overall population. However, they not defined SCAP.

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A recent meta-analysis by Siemieniuk *et al*.[8] showed that the use of systemic corticosteroids in CAP may reduce mortality, need for mechanical ventilation, development of ARDS, and with high certainty a reduction in time-to-clinical stability and duration of hospitalization. In a subgroup of SCAP patients, the study also showed a possible reduction in mortality.

The major problems with data about systemic corticoids therapy in these human trials are because they included many patients with low severity, therefore, these patients have a low mortality and consequently, it is very difficult to demonstrate differences in important clinical outcomes such as treatment failure and mortality. Another point is that some patients are included regardless the initial level of inflammation. We should remember that the rationale for use steroids in CAP is the presence of high inflammatory response of the patients. Up to now this variable has not been taken into account in the majority of human trials. Patients with a high inflammatory response have higher rates of treatment failure[9] and mortality.[10] Furthermore, the dosages, the type and the length of treatment are very different among trials, which makes very difficult to establish comparisons among them. Finally, 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."

We recently published a trial in SCAP patients[11] comparing methylprednisolone (0.5 mg/kg BID during 5 days) versus placebo, with important differential characteristics. Our definition of SCAP applied for patients with modified American Thoracic Society criteria, or with pneumonia severity index risk Class V. We included patients with a high systemic inflammatory response, (C-reactive protein [CRP] ≥15 mg/dL). Because treatment failure in, CAP is associated with higher mortality.[12] Our primary endpoint was treatment failure rather than mortality. We defined treatment failure as early (clinical deterioration indicated by the development of shock, need for invasive

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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 h and 120 h after treatment initiation). In our trial, we monitored the systemic inflammatory response using different biomarkers such as CRP, procalcitonin, tumor necrosis factor-alpha, and interleukins 6, 8, and 10, until day 7 after the inclusion of patients in the trial.

Our results showed a decrease from 31% to 13% in the treatment failure rate ($P = 0.02$) of our population. This reflects that corticosteroids reduced the risk of treatment failure with an odds ratio of 0.34. Mortality did not differ significantly between groups (10% in the methylprednisolone arm *vs.* 15% in the placebo arm $P = 0.37$). This reduction in treatment failure was more evident in late treatment failure (3% *vs.* 25%; $P = 0.001$), and especially in radiographic progression, (2% *vs.* 15%; $P = 0.007$). The rates of side effects were not important and similar between arms.

The long-term recruitment period, 8 years, and the use of methylprednisolone for 5 days only with an abrupt interruption of the treatment were potential pitfalls of our study. However, we monitored proinflammatory biomarkers until day 7, and we did not find a rebound of the inflammatory response.

With this results, we believe that less treatment failure, particularly late, and less radiographic progression can be due to stopping a progression to ARDS or a potential blocking of the Jarisch–Herxheimer reaction, which is thought to be due to high concentrations of cytokines release after the initiation of antibiotics, possibly through the release of endotoxin, or other bacterial mediators in patients with high bacterial burden.

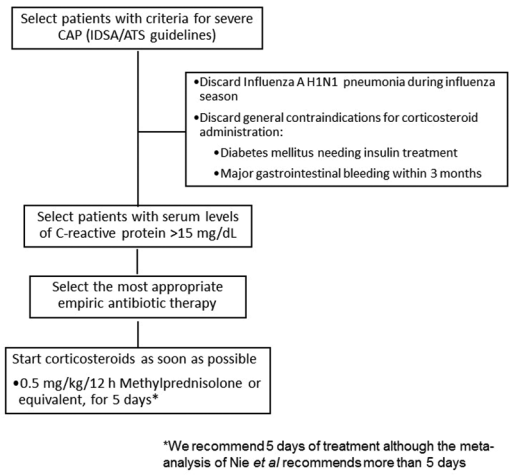

Figure 1: Proposed algorithm for the use of corticosteroids

We believe that it is time to start introducing treatment with corticosteroids in the clinical practice in severe CAP. We recommend selecting SCAP patients with high inflammatory response measured by CRP. We need to exclude patients with influenza pneumonia as we did in our trial since there are increasing evidence that corticosteroids increase mortality in influenza pneumonia.[13] We do not have information on the possible effect of corticosteroids in other viral pneumonias.[14] However, a high serum level of CRP indicates that pure viral pneumonia is unlikely. A proposed algorithm for the use of corticosteroids as adjunctive treatment for CAP is shown in Figure 1.

In conclusion, after discussion these results, we believe that corticosteroids can help to decrease treatment failure and probably mortality in SCAP patients. A high systemic inflammatory response and to discard influenza pneumonia are the two important premises for their utilization.

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