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What's new in severe community-acquired pneumonia? Corticosteroids as adjunctive treatment to antibiotics

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Severity criteria occur in up to 18 % of hospitalized patients with community-acquired pneumonia (CAP), and still carry a high morbidity and mortality. In a French multicentre study on severe pneumococcal CAP admitted to intensive care units (ICU), the overall mortality rate was 29 %, with high proportions of patients in septic shock and needing mechanical ventilation [1]. Patients with severe CAP (SCAP) 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, sepsis and end-organ dysfunction [2].

Systemic adjunctive corticosteroid therapy attenuates the local and systemic inflammatory response [3], and may potentially decrease the development of acute respiratory distress syndrome (ARDS), sepsis and mortality. In a 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 [4].

In humans, several randomised clinical trials (RCT) have been performed mostly in hospitalised patients with non-SCAP. A meta-analysis [5] showed that steroids reduced mortality in the subgroup of patients with SCAP but not in the overall population. However, SCAP was not defined. Another more recent meta-analysis [6] showed that the use of systemic corticosteroids in CAP was associated with moderate reduction in the need for mechanical ventilation and development of ARDS, and, with high certainty, a reduction in time to clinical stability and duration of hospitalisation. The study also showed a possible reduction in mortality, but this effect was seen mainly in the subgroup of patients with SCAP. The last meta-analysis classified CAP studies as 'severe' when >70 % patients had baseline severe pneumonia, or if mortality was ≥15 % in the control arm when severity at presentation was not available.

Several pitfalls have occurred in most of these RCTs. First, the inclusion of many patients with low severity. These patients have a low mortality and, consequently, it is very difficult to demonstrate differences in important outcomes such as treatment failure and mortality. Second, inclusion of patients regardless of the initial level of inflammation. According to the rationale of using steroids in CAP, a high inflammatory response is advisable to use this treatment. Up to now, this variable has not been taken into account in the majority of RCTs. Patients with a high inflammatory response, i.e. high levels of C-reactive protein (CRP), have higher rates of treatment failure [7] and mortality [8]. Third, the dosages, the type and the length of treatment are very different among RCTs, which makes it very difficult to establish comparisons between them. Fourth, 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". The first one depends on other variables, and the second is driven by the persistence of fever which in fact is down-regulated by corticosteroids.

We performed a RCT [9] comparing methyl-prednisolone (0.5 mg/kg b.i.d. for 5 days) versus placebo,

with important differential characteristics. First, we only included SCAP patients with modified American Thoracic Society criteria, or with Pneumonia Severity Index (PSI) risk class V. Second, we chose patients with a high systemic inflammatory response (CRP > 15 mg/dL). Third, rather than mortality as a primary end-point, we chose treatment failure. Treatment failure in CAP is associated with higher mortality [10]. 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). Fourth, we monitored the systemic inflammatory response using different biomarkers such as CRP, Procalcitonin, tumour 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 ($P = 0.02$). In other words, 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 were similar between arms.

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

In agreement with the editorial comment accompanying the article [11], 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.

We really think 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 is increasing evidence that corticosteroids increase mortality in influenza pneumonia [12]. We do not have information on the possible effect of corticosteroids in other viral pneumonias caused by adenovirus, rhinovirus, respiratory syncitial virus, or others such as MERS [13]. 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 Fig. 1.

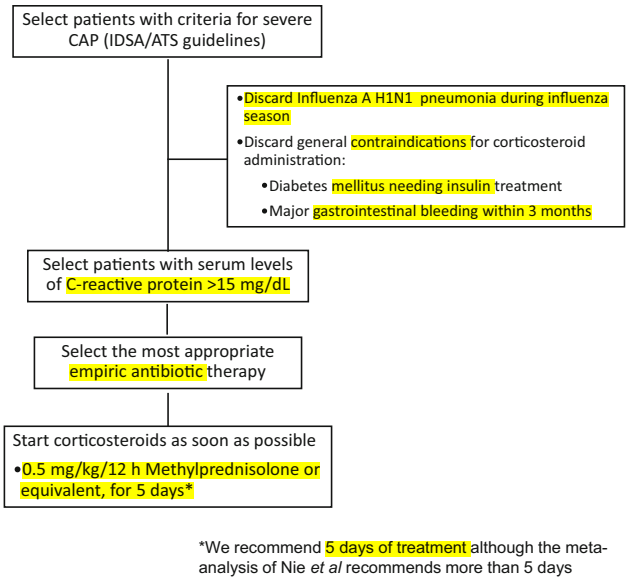

Fig. 1 Steps for the administration of corticosteroids in severe community-acquired pneumonia. * See [5]. *IDSA* Infectious Disease Society of America, *ATS* American Thoracic Society [14]

In summary, we believe that corticosteroids are useful in SCAP and can help to decrease treatment failure and probably mortality. The two important premises for their utilisation are a high systemic inflammatory response and to discard influenza pneumonia.

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