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Corticosteroids for Pneumonia: Are we there yet?

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Community acquired pneumonia (CAP) is the most important respiratory infection and the leading cause of death from infectious disease around the world. Mortality from pneumonia has not varied over the past decades despite the use of antimicrobial agents (1). Strategies targeted to modulate the immune response seem to be a feasible and promising alternative to antimicrobials for patients with pneumonia. The administration of corticosteroids as an immunomodulatory agent may potentially improve clinical outcomes in patients with pneumonia (2).

Corticosteroids inhibit the expression and action of many molecules involved in the inflammatory response associated with pneumonia. The molecular mechanisms associated are many and include transactivation by increasing the gene transcription of anti-inflammatory molecules (3). In addition, corticosteroids can cause transrepression by decreasing gene transcription of different inflammatory cytokines, chemokines or adhesion molecules (3). Experimental studies have shown that corticosteroid administration reduces the inflammatory response in severe CAP (4). However, limited clinical data are available to support the use of corticosteroids in clinical practice.

In this *Respirology* issue Polverino et al. (5) describe the observational experience on the use of corticosteroids in the setting of community acquired pneumonia. We believe it is important to place this study in context with prior literature on the topic. In a small pilot study of patients with pneumonia requiring mechanical ventilation, Monton et al. (6) found an immunosuppressive effect of the use of corticosteroids and a trend towards lower mortality among corticosteroid treated patients. Garcia-Vidal et al. (7) performed a retrospective cohort study in 308 hospitalized patients with severe CAP. The authors found that corticosteroid administration was associated with a lower mortality compared to non-corticosteroid treated patients. Several randomized control trials have shown conflicting

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results in different pneumonia populations. Confalonieri et al. (8) assessed the efficacy and safety of the administration of a continuous infusion of hydrocortisone in 46 patients with CAP requiring ICU admission. The authors demonstrated that pneumonia patients treated with corticosteroids had a mortality reduction and a significant improvement in the main clinical endpoints, such as chest x-ray, organ dysfunction, oxygenation ratio and ICU and hospital stay. However, the small sample size and differences among groups at admission limits the generalizability of these results. In addition, Snijders et al. [9] found no differences in 30-day mortality, time to clinical stability, and length of hospital stay among hospitalized CAP patients (n=213) treated randomly with corticosteroids compared to placebo. However, late clinical failure occurred more frequently in the corticosteroid group. Meijvis et al. [10] evaluated the clinical efficacy of corticosteroids administered in the first four days of admission versus placebo in 304 patients with pneumonia. They found no differences in clinical outcomes including in-hospital mortality, ICU admission and severe adverse events. However, patients treated with corticosteroids had a shorter length of hospital stay. Fernandez-Serrano et al. (11) described that in 56 hospitalized CAP patients treated with antibiotics in combination with methylprednisolone experienced an improvement in respiratory failure rates and accelerated the timing of clinical resolution. Recently, Salluh et al. (12) presented data on severe CAP (n=111) patients requiring invasive mechanical ventilation treated with systemic corticosteroids. The administration of adjunctive corticosteroid therapy did not influence intensive care unit and hospital mortality, withdrawal of vasopressors, and organ failure recovery. Therefore, it is unclear what kind of patients with pneumonia may benefit from the administration of systemic corticosteroid.

The manuscript by Polverino and colleagues (5) published in this *Respirology* issue, studied a large prospective observational cohort of 3,257 adult patients with CAP admitted to a university hospital in Barcelona, Spain. Among these, 260 patients (8%) received systemic corticosteroids on admission. The authors attempted to understand the clinical conditions associated with the use of corticosteroids in patients with CAP and the impact of corticosteroids on clinical outcomes. After a thorough statistical analysis, Polverino et al. (5) found that chronic respiratory conditions and high severity of illness at clinical presentation were associated with the use of corticosteroids. Patients who received corticosteroids had a longer length of hospital stay (LOS) (9 days vs. 6 days, $p<0.01$) and were more likely to require mechanical ventilation (10.8% vs. 6.5%) during hospitalization. In addition, administration of systemic corticosteroids was the main risk factor for prolonged LOS in the multivariate analyses (OR 2.01, 95CI 1.29-3.14, $p<0.01$). However, CAP patients treated with corticosteroids had higher severity of illness on admission, but did not have any differences in mortality or time to clinical stability compared to patients who did not receive corticosteroids. Several findings from Polverino et al. (5) need further discussion. First, the authors found that patients with chronic respiratory diseases, such as COPD were more likely to receive systemic corticosteroids. It is unclear if the presence of bronchospasm at the time of clinical presentation motivated clinicians to use systemic corticosteroids in these patients with pneumonia. This indication bias is usually avoided in randomized control trials, that systematically excludes patients with any acute condition requiring corticosteroids such as bronchospasm (9), or a condition in which systemic corticosteroid administration is recommended for patients with acute asthma or COPD (8,11). It is important to recognize that the authors conscientiously excluded chronic outpatient corticosteroid therapy administration. Second, the prior literature suggested that patients with severe pneumonia may benefit from the administration of corticosteroids. The study by Polverino et al. (5) revealed that despite higher severity of illness at initial presentation, mortality was not higher among corticosteroid users. The lack of effect may suggest a moderate protective effect by the administration of corticosteroids, as observed in other trials mentioned above. Large and well design randomized control trials may be able to address this concern particularly among severely ill patients with CAP. Finally, the most

important observation described by the present study, that patients treated with corticosteroids have longer hospital length of stay may have important morbidity implications. The potential morbidity implications by the longer length of hospitalization include higher cost of care and the risk of acquiring hospital complications. This important finding is in contrast to the study by Meijvis et al. (10) that showed a shorter length of hospital stay.

In conclusion, the study by Polverino et al. (5) contributes to the understanding of the use of corticosteroids in the real world setting, but randomized control trials are needed to further assess the risk-benefit ratio of corticosteroids for patients with community-acquired pneumonia.

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