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EDITORIAL

Using Steroids in Patients with Community-Acquired Pneumonia at the University of Louisville Hospital: Who, What, and When

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Introduction

There is a consensus regarding the need to move beyond antibiotic therapy if we want to improve outcomes of hospitalized patients with community-acquired pneumonia (CAP). However, there is a lack of consensus regarding the use of steroids as adjunctive therapy in patients with CAP.

Eleven meta-analyses have been already published in the field of steroids and CAP [1-11]. A primary problem with several of these meta-analyses is the inclusion of studies with important methodological weaknesses. In addition, in a recent meta-analysis which was published in the American Journal of Emergency Medicine [10], the authors incorporated 3 manuscripts which were written in Chinese, making it impossible for us to evaluate the quality of those research studies. At present, we have more meta-analyses published on the topic of steroids and CAP than original randomized clinical trials (RCTs), with some of them arriving to different conclusions. Meta-analyses are considered the highest level of evidence when they are based on high-quality RCTs, but this is not the case in the field of steroids and CAP. Because of the above, the controversy regarding the use of steroids in patients with CAP will continue until further high quality research is published.

With all these caveats in mind, after reviewing recent randomized clinical trials [12-19] we consider that there is enough evidence to recommend the use of steroids only in a well selected group of hospitalized patients with CAP. We also consider that the current level of evidence in favor of steroid is weak, and that there is a significant possibility that future studies may alter our current recommendations. In this editorial, we summarize our approach to the use of steroids in hospitalized patients with CAP at the University of Louisville Hospital.

Who are the candidates for steroid therapy?

Different studies have used different inclusion criteria to define a patient as a candidate for steroid therapy. Steroids are supposed to improve outcomes by controlling an exaggerated or dysregulated host inflammatory response. Hospitalized patients

with CAP with exaggerated or dysregulated inflammation are likely to present with severe CAP with clinical and laboratory evidence of sepsis. Translating these concepts into clinical practice, we consider patients as candidates for steroid therapy if they have clinical or laboratory manifestations compatible with early sepsis. Clinically, the patient may have respiratory failure requiring ventilator support or the need for high FIO₂ (>50%), hypotension unresponsive to fluid resuscitation, or evidence of newly developed organ dysfunction. Elevated levels of C-reactive protein (CRP) have been associated with high cytokine levels in patients with CAP [20]. Elevated levels of lactic acid and or the presence of metabolic acidosis are associated with sepsis and poor outcomes in patients with CAP [21,22]. Based on the above, from a laboratory perspective, we consider patients as candidates for steroid therapy if they have CRP greater than 150 mg/L, lactic acid greater than 4 mmol/L, or arterial pH is lower than 7.30. There are no clinical or laboratory criteria that are diagnostic of sepsis, then the presence of any criteria to support diagnosis of sepsis should not be clearly explained by an alternative clinical diagnosis.

In an attempt to limit steroid adverse events, most clinical studies excluded patients who are at risk for adverse events. After reviewing exclusion criteria from all studies, we recommend that patients will not be candidates for steroid therapy if they have a recent history of gastrointestinal bleeding, uncontrolled diabetes, or if they are severely immunocompromised.

Retrospective studies reported that the use of steroids in patients with influenza pneumonia is associated to worse clinical outcomes [23,24]. The presence of influenza as etiology of CAP was used as an exclusion criterion in some of the clinical trials of steroid use in hospitalized patients with CAP. Production of Interferon-gamma (IFN- γ) interferes with replication of influenza and other viruses [25]. It can be speculated that steroids, by inhibiting IFN- γ , may facilitate viral replication in patients with influenza CAP or in any other form of viral CAP. Until further studies define the role of steroids in patients with CAP of viral etiology, we recommend that these patients should not be considered candidates for steroid use. If a patient is seen in the emergency room with a clinical and laboratory picture compatible with CAP and exaggerated inflammatory response, we recommend not to wait for microbiological tests to define if viral CAP is present. If after initiation of steroid therapy, the microbiological workup indicates viral CAP, steroids can be discontinued at that point.

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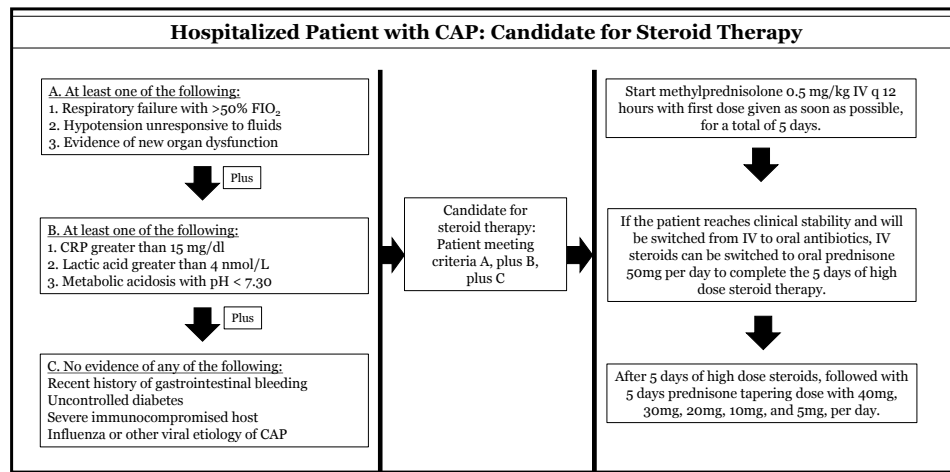


Figure 1 Criteria to define a patient as a candidate for steroid use and suggested course of therapy.

What steroids should be used, and for how long?

Investigators have used different types of steroids, different doses and different duration of therapy. In an attempt to obtain early maximal effect, we consider initially the use of the intravenous route, even in patients who are able to take oral medications. Our recommendation is to use methylprednisolone 0.5 mg/kg IV every 12 hours for 5 days. If a patient has a rapid improvement, reaches clinical stability, and antibiotic therapy is switched from intravenous to oral, we recommended at that point to switch from intravenous methylprednisolone to oral prednisone 50mg daily to complete the 5 days of therapy.

A rapid discontinuation of steroid therapy in patients with severe CAP may produce a rebound of the inflammatory response. We are participating in the current US Department of Veterans Affairs trial of steroids in patients with CAP admitted to the ICU, the Extended Steroid in CAP (ESCAPE) study (NCT01283009). In this study, after initial high dose, steroid dose is tapered in an attempt to prevent rebound inflammation. Considering the above, we recommend a total of 10 days of steroids. Initial five days of high dose steroids with a tapering dose of prednisone for the following 5 days with doses of 40mg, 30mg, 20mg, 10mg, and 5mg per day.

When steroid therapy should be administered?

In patients with *Streptococcus pneumoniae* meningitis, the use of antibiotic therapy may be followed by an exaggerated inflammatory response due to destruction of bacteria and the release of intracellular toxins and antigens into tissues. Patients with *Streptococcus pneumoniae* meningitis are recommended to be given steroids before or concurrently with antibiotic administration [26]. In HIV patients with *Pneumocystis jirovecii* pneumonia (PCP), the killing of the organism may produce increased inflammation. In this clinical scenario steroids are also recommended concurrently with PCP therapy [27]. In a recent publication, we documented that patients with CAP in whom macrolides are given before beta-lactam antibiotics have better clinical outcomes than patients treated with macrolides after beta-lactams, suggesting that the

same phenomenon described in *Streptococcus pneumoniae* meningitis and PCP may be occurring in patients with CAP [28]. Our recommendation is to administering steroids concurrently with antibiotics or as soon as possible once a patient has been identified as a candidate for steroid therapy. The initial treatment for severe CAP is commonly implemented by emergency medicine physicians or hospitalists even if patients are subsequently admitted to the ICU. It is thus important for these clinicians to be updated with the current literature on steroids and CAP.

Conclusion

Steroids may improve clinical outcomes in hospitalized patients with CAP who have an exaggerated inflammatory response. Based on our analysis of the current evidence, the flowchart presented in **Figure 1** was developed as a guideline for the identification of patients who may benefit from steroid use. Until further RCTs are published, practitioners should continue to use clinical judgment, weight potential benefit and risk, and define if the individual patient is a candidate for steroid use.

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