

Adjunct corticosteroid treatment in patients with pneumonia: A precision medicine approach

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ABSTRACT

Pneumonia is the leading infectious cause of death worldwide. While inflammation is critically important in host response to microbial invasion, exaggerated inflammation can damage the lungs, contributing to respiratory failure and mortality. Corticosteroids are effective in reducing inflammation and can also cause immune suppression. Presently, clinicians are unable to reliably distinguish between exaggerated and appropriate immune response and thus cannot rapidly identify patients most likely to benefit from adjunctive corticosteroids. In this review, we propose a biomarker-guided, precision medicine approach to corticosteroid treatment, aimed to give these medications at appropriate dose and time and only to patients who have exaggerated inflammation.

KEY WORDS: Pneumonia; corticosteroids; C-reactive protein; biomarkers; intensive care unit; ICU

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INTRODUCTION

Pneumonia is one of the ten leading causes of death worldwide, with mortality rates ranging from 5% to 15% in hospitalized patients and rising up to 30% if the patients are admitted to intensive care unit (ICU) [1,2]. Increased levels of pro-inflammatory mediators are a prominent feature of pneumonia and exaggerated inflammatory response can injure the lungs contributing to worsening respiratory failure and mortality. While adjunct corticosteroid treatment can effectively reduce inflammatory response, the use of corticosteroids in critically ill patients with pneumonia is variable due to an inability to identify patients who will benefit.

The importance of local and systemic inflammation in patients with pneumonia

Lung defense mechanisms are defined by their anatomic, mechanical, humoral, and cellular components. Alveolar macrophages play the key role in inflammatory response due

to their ability to respond to bacterial exposure and to recruit polymorphonuclear leukocytes [3]. Different combinations of cytokines are produced during different inflammatory conditions [4-6]. Interleukin (IL)-6 is the major inducer of most acute phase responses, along with IL-1 beta, tumor necrosis factor (TNF)-alpha, and interferon gamma [7]. IL-1 beta and TNF-alpha are considered endogenous toxins, bacterial toxins, as well as exogenous pyrogens. As such, IL-1 beta and TNF-alpha lead to an appearance of the clinical hallmarks of acute inflammation such as: 1) fever and accelerated release of leukocytes into circulation, 2) hepatic synthesis of acute phase proteins, such as C-reactive protein (CRP), 3) synthesis of adhesion molecules, and 4) neutrophil degranulation.

CRP has both pro-inflammatory and anti-inflammatory actions, although the primary effect may be an anti-inflammatory one [8,9]. CRP can promote recognition and elimination of pathogens, and it can enhance clearance of necrotic and apoptotic cells [10-16]. The major function of CRP is its ability to bind phosphocholine, thereby permitting recognition of both foreign pathogens that display this moiety and phospholipid constituents of damaged cells [12]. Pro-inflammatory effects of CRP include: 1) activation of the complement system, 2) induction of monocytes of inflammatory cytokines,

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3) induction of tissue factors [17,18], and 4) shedding of the IL-6 receptor [19].

Subclinical or low-grade inflammation is defined as a condition in which CRP concentrations range between 3 mg/l and 10 mg/l. Unlike acute inflammation, low-grade inflammation occurs in many conditions in which there are low degrees of metabolic dysfunction. The main purpose of low-grade inflammation is the restoration of metabolic homeostasis [20]. In contrast, high systemic inflammation is defined as a condition in which CRP concentration is ≥ 150 mg/l [21].

Furthermore, diagnoses of nosocomial pneumonias, such as hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP), also rely on CRP levels. In a recent study detailing a time-dependent analysis of the relative CRP concentration in VAP, CRP levels were shown to be significantly higher as early as day 4 in VAP patients with a poor outcome compared to those with a good outcome. The established sensitivity of CRP values to antibiotic treatment makes CRP a useful predictor of the clinical course of a disease [22]. CRP concentrations have a tendency to decline between days 1 and 7 in all VAP patients but are significantly higher in patients with unfavorable disease outcomes [23].

Reducing acute inflammation with adjunctive corticosteroid treatment

In many infectious diseases, particularly in those affecting the central nervous system as well as in those affecting the lower respiratory tract, antimicrobial treatment alone falls short in curbing exaggerated local and systemic inflammation. The resulting progression to organ failures and fatal outcomes has prompted many scientific investigations into the role of anti-inflammatory treatment strategies for the treatment of the exaggerated local and systemic inflammation. In particular, corticosteroids appear to be the most studied pharmacological therapy in these conditions. Systemic adjunctive corticosteroid therapy attenuates the local and systemic inflammatory response, inhibits expression of pro-inflammatory cytokines, and accelerates expression of anti-inflammatory cytokines [24]. In addition, glucocorticosteroids appear to cause depression of phagocytic function of alveolar macrophages and neutrophils, decrease mobilization of inflammatory cells into areas of infection, and cause alterations in antigen presentation and lymphocyte mobilization, giving them an important role in the pathogenesis of pneumonia. These effects increase the risk of bacterial and fungal infections and they may contribute to further morbidity and mortality [25].

However, several meta-analyses imply that the use of adjunctive glucocorticoid therapy outweighs possible harms in patients with community-acquired pneumonia (CAP), who are at a high risk of mortality as a result of sepsis or respiratory

failure. These patients have a FiO_2 requirement of $>50\%$ as well as one or more of the following features: 1) metabolic acidosis with an arterial pH of <7.3 , 2) lactate value of >4 mmol/l, and 3) CRP concentration of >150 mg/l. In these patients, the following risk factors are excluded: 1) recent gastrointestinal bleeding, or 2) severe immunocompromise. As corticosteroid use is known to cause prolonged viral shedding, these drugs cannot be applied for the treatment of viral pneumonia and glucocorticoids should be avoided in patients with CAP if it is known to be caused by a viral or a fungal pathogen [26-28].

Adverse effects of glucocorticosteroids arise due to their effect on innate and acquired immunity that predisposes older patients and those with lower functional status to infection. However, they may not manifest any signs and symptoms of infection due to the inhibition of cytokine release and associated reduction in inflammatory and febrile responses [29]. Up-to-date findings suggest that a prolonged use of glucocorticoids in addition to other immunosuppressant drugs, in patients with underlying immunosuppressive conditions, lead to opportunistic infections with organisms of low pathogenicity. For example, a pneumonia caused by *Pneumocystis jirovecii* is associated with the use of glucocorticoids - both with chronic use of moderate doses of glucocorticoids and with short-term use of high doses of glucocorticoids [30].

Etiologies of acute respiratory distress syndrome (ARDS) with underlying steroid-responsive acute eosinophilic pneumonia or steroid reactive process CAP should be treated with systemic glucocorticoids, but their administration to patients with ARDS from other causes is controversial [31].

Although glucocorticoids have been demonstrated to decrease the duration to shock reversal in patients with septic shock, their role in the management of severely injured patients is still ill-defined and, therefore, in these patients, glucocorticoids do not represent the standard therapy [32,33].

Adjunctive corticosteroid treatment in pneumonia

Antibiotics are the mainstay treatment for bacterial pneumonia. Even though studies have reported that early antibiotic initiation in the treatment of bacterial pneumonia is beneficial, some experts argue that an independent risk factor should be identified in order to begin the antibiotic treatment. Nevertheless, it should be emphasized that the delay in antimicrobial therapy for seriously ill patients could adversely affect the treatment success.

There are no clear recommendations on the use of adjunctive corticosteroids as an additional therapy in pneumonia treatment due to the controversial results obtained in different clinical trials. The rationale for the use of corticosteroids in pneumonia treatment is the presence of high inflammatory response. However, to date, this variable has not been

considered a valuable characteristic for monitoring in the majority of human clinical trials. Furthermore, patients with high inflammatory responses have higher rates of treatment failure and mortality [34,35]. Considering that there have been significant differences in corticosteroid dosage, the type of corticosteroid being investigated and the length of corticosteroid treatment among different clinical trials, it is very difficult to compare their results. Due to the strong immunosuppressive effect of corticosteroids, their role in acute inflammation is still questionable. However, several multicenter, randomized, and controlled trials have shown that oral corticosteroids, as adjunctive therapy in pneumonia treatment, have significant benefits including the ability to achieve rapid clinical stabilization of hospitalized patients [36]. Moreover, lower treatment failure, as well as faster radiological regression, is achieved when adding corticosteroids to a therapy [37]. In addition, it is important to emphasize that no severe adverse effects have been recorded in association with corticosteroid use [38].

Corticosteroid use in critically ill patients with pneumonia

Treatment of infections in ICUs is especially challenging. Intensivists are often faced with clinical deterioration of patients despite providing timely and adequate therapy. Corticosteroids are commonly used in critically ill patients with refractory septic shock and ARDS, but they do not represent a standard treatment of sepsis or pneumonia, due to limited evidence of their efficacy. A study published by Confalonieri et al. recommends corticosteroid use in critically ill patients [39]. The administration of corticosteroids in these cases leads to improvement of PaO₂/FiO₂ ratio in mechanically ventilated patients as well as decreased ICU mortality and hospital length of stay [39]. Patients who are hemodynamically unstable can also benefit from adjunct corticosteroid therapy, as it has been shown in a study published by Tagami et al. [40]. They concluded that low-dose corticosteroids in patients on vasoactive support lead to substantially reduced 28-day mortality [40]. Other clinical trials did not demonstrate that corticosteroids provide significant benefit [27]. Recent guidelines published by the Society of Critical Care Medicine (SCCM)/European Society of Intensive Care Medicine (ESICM) cautiously

recommend the use of corticosteroids in the treatment of CAP and ARDS, thereby underscoring limited evidence to support this recommendation [41]. Benefits of given corticosteroid therapy as well as side effects are shown in Table 1.

The use of corticosteroids in the treatment of pneumonia is largely determined by the severity of respiratory illness. While excessive inflammation can be a major contributor to the overall severity of the illness, many other factors contribute to it as well. For example, in morbidly obese patients, lying in a recumbent position will markedly worsen the degree of hypoxemic respiratory failure. However, these patients may not necessarily have a high inflammatory response and may even be immunosuppressed. Similarly, the patient with pneumonia and a hyperinflammatory phenotype may have only a mild degree of hypoxemia, at least in the early stage of the illness. Unfortunately, some patients are unnecessarily exposed to adverse effects of steroids while, in others, a delay in a steroid administration can lead to a worsening of the disease.

Individualized, biomarker-guided corticosteroid treatment

In the current clinical practice, corticosteroids are used in a disorganized way, with arbitrary dosing regimens irrespective of the degree of inflammation. There are no clear indications regarding the start of corticosteroid treatment, an increase or a decrease in the dosing, nor regarding the discontinuation of corticosteroid treatment. This variability in the use of corticosteroids, however, presents an opportunity to examine how steroid treatment can be optimized and tailored to those patients who may benefit the most. A proposed algorithm is shown in Figure 1.

Recent research studies used biomarker panels consisting of multiple inflammatory markers to identify distinct hyperinflammatory endophenotypes [42]. Although accurate and validated, the availability and slow turnaround time make multiple biomarker panels impractical for the current clinical use. CRP concentration values are easily obtainable in the current clinical practice compared to other biomarkers whose values are more difficult to obtain outside of basic research setting. CRP is an acute phase reactant and a commonly used marker of increased inflammation in patients

TABLE 1. Benefits and side effects of corticosteroid therapy in critically ill patients with pneumonia

Pro	Against
Faster radiological regression	Limited evidence, cautiously recommended by SCCM/ESICM
Improvement of PaO ₂ /FiO ₂ ratio in mechanically ventilated patients	Dosage and length of treatment not standardized
Reduced need for mechanical ventilation	Increased risk for hyperglycemia
Prevention of ARDS	Questionable immunosuppressive effect in acute inflammation
Decrease in ICU mortality and hospital stay	
Reduced 28-day mortality in patients with vasoactive support at the ICU admission	

ICU: Intensive care unit; ARDS: Acute respiratory distress syndrome; SCCM: Society of Critical Care Medicine; ESICM: European Society of Intensive Care Medicine

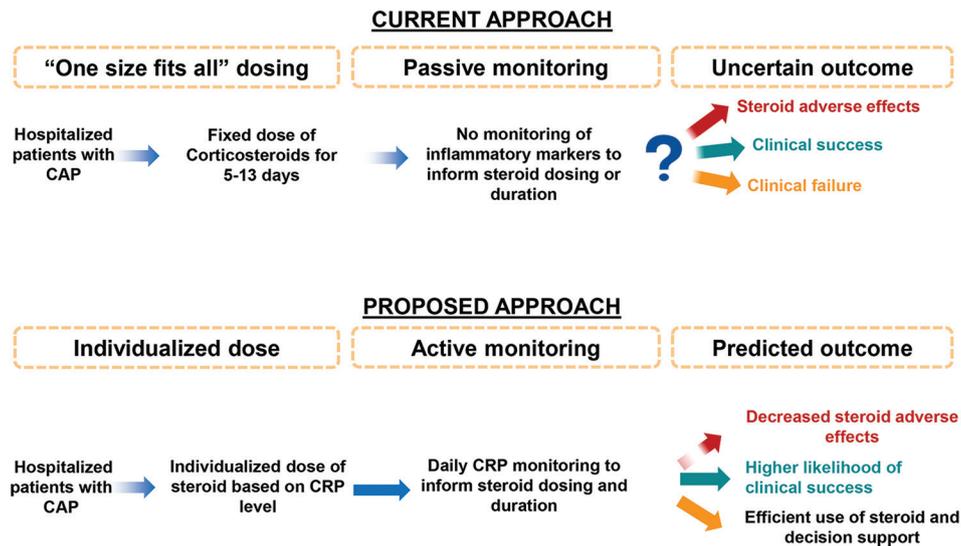


FIGURE 1. Adjunct corticosteroid treatment in patients with pneumonia: a proposed precision medicine approach.

with lower respiratory tract infections [43]. High CRP values are associated with an increased rate of mortality and pneumonia severity [44].

Recently, studies investigating the treatment of pneumonia have utilized CRP values in order to more accurately define a population that may benefit from corticosteroids [37]. This enrichment strategy suggested that patients with a high inflammatory response (pneumonia with an admitting CRP >150 mg/l) may benefit from a modest dose corticosteroid administration [37]. Expert recommendations also favor the use of glucocorticoids in patients with pneumonia who have evidence of an exaggerated or dysregulated host inflammatory response (sepsis or respiratory failure) with a CRP >150 mg/l [45].

CONCLUSION

In this review article, we propose a biomarker-guided, precision-medicine approach to corticosteroid treatment in order to prescribe these medicines in a timely and appropriate dosing to patients with an exaggerated inflammation. Further research is needed to define optimal timing, dose, and duration of adjunct corticosteroid treatment and to evaluate the effect of an individualized, biomarker-guided approach on patient-important outcomes.

DECLARATION OF INTERESTS

The authors declare no conflict of interests.

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