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Corticosteroids for Community-Acquired Pneumonia

Overstated Benefits and Understated Risks

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At a recent international clinical meeting, we presented the case of an elderly woman with community-acquired pneumonia (CAP), clearly sick enough to require hospitalization but not meeting any criteria for being classified as "severe" and clearly not needing consideration of intensive care. Using an audience response system, nearly one-half of those in the audience, predominantly pulmonologists, indicated they would routinely give such a patient corticosteroids at a dose of 50 mg of prednisolone per day. This response is extremely disturbing because the routine use of systemic corticosteroids in such a patient is way beyond what the available evidence supports and shows significant overestimation of the benefit and underestimation of the risk of such an approach. In this commentary, we outline the current evidence base for corticosteroids in CAP in the hope that clinicians will reassess what has become a potentially dangerous practice.

It is understandable why clinicians might wish to use unproven therapy for patients with CAP. Despite improvements in the outcomes of patients with CAP during the last two decades,[1,2] CAP continues to exact a tremendous toll of morbidity and mortality.[3] Because most in-hospital CAP deaths are not related to lapses in the quality of care,[4] we will not improve outcomes further by giving more appropriate antibiotics or giving them faster. There is a good pathophysiologic basis for believing that if we can modulate the body's inflammatory response to infection, we can improve CAP outcomes. Inflammation drives sepsis and septic shock, and contributes to other adverse outcomes, including cardiovascular events.[5,6] Because corticosteroids are some of the most potent antiinflammatory agents we have, and they have shown benefit in pneumococcal meningitis,[7] it is reasonable to test the hypothesis that they might improve CAP outcomes.

A number of small studies have attempted to assess the utility of corticosteroids in CAP, and there are now more published meta-analyses[8-19] than there are primary studies. The general, but not universal, consensus of these meta-analyses has been that glucocorticoids reduce mortality in severe CAP but not in nonsevere CAP. One of the

ABBREVIATIONS: ATS = American Thoracic Society; CAP = community-acquired pneumonia

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most recent and most rigorously performed of the meta-analyses, published by the Cochrane group,[12] reported a risk ratio for mortality of 0.58 (95% CI, 0.40-0.84) associated with corticosteroid use for severe CAP. There was no evidence of benefit in patients with nonsevere CAP (risk ratio, 0.95; 95% CI, 0.45-2.00). Despite the improved mortality reported in patients with severe CAP, it is, however, critically important that clinicians understand the limitations of the evidence base for glucocorticoids in CAP and how the meta-analyses have failed to properly critique the studies included. Perhaps even more importantly, clinicians should be aware that there is no credible evidence of improved outcomes in patients with nonsevere CAP (patients like the one described in the first paragraph of this commentary).

The major driver of a mortality advantage in all the meta-analyses is Nafae et al.[20] This study, published in the *Egyptian Journal of Chest Diseases and Tuberculosis* in 2013, was a single-center, single-blind trial in adults with CAP. Sixty patients were randomized to receive corticosteroids and 20 to receive placebo. The authors reported a mortality benefit in the steroid group (6.7% vs 31.6%; $P < .05$). There are, however, two very significant problems with this study. Although the paper states that randomization was stratified according to severity, no details of the stratification are provided, and severity details are generally lacking. More importantly, although the authors report no significant differences in baseline characteristics between the groups, re-analysis of the table provided (assuming a normal distribution given that they provide t-scores) shows a very significant difference in the degree of renal impairment at randomization in the placebo group compared with the corticosteroid group: creatinine, mean ± SD, 1.5 ± 0.8 mg/dL vs 1.14 ± 0.5 ($P = .02$); urea, 41.8 ± 19.5 mg/dL vs 31.4 ± 14.2 mg/dL ($P = 0.01$), respectively. It is hardly surprising that a group of patients with normal renal function at enrollment did better than a group with significant renal impairment.

There are also significant problems with imbalance at baseline with a second study, Sabry and Omar.[21] Eighty patients were randomized on a 1:1 basis in this multicenter, double-blind, placebo-controlled trial in adults with severe CAP according to American Thoracic Society (ATS) criteria.[22] First, mortality was measured at day eight, not at end of hospitalization, demonstrating a statistically nonsignificant trend toward lower mortality in the steroid group (38 vs 34; $P = 0.3$). Second, although the authors report no significant differences in the patient groups at baseline, their table shows 34 of 40 patients in the placebo group requiring mechanical ventilation at baseline (85%), compared with only 26 of the 40 patients in the steroid group (65%). The authors report the *P* value as .144; however, by χ^2 testing it is .04, and by the Fisher exact test it is .07. With 20% more patients requiring mechanical ventilation at study entry, any trend to improved mortality must be highly suspect.

The only study other than Nafae et al[20] to show a mortality benefit for steroids is Confalonieri et al.[23] This multisite trial included patients with severe CAP according to the 1993 ATS criteria.[24] The trial was terminated early following randomization of 46 patients (23 in each group) due to a significant difference in mortality (7 [30%] vs 0; $P = .009$). This paper has been identified as a significant outlier by a number of authors, including one meta-analysis.[10,25] In particular, the zero mortality in the steroid group is not remotely likely to be reproducible. Differences in clinical care such as greater use of noninvasive ventilation at baseline in the steroid group (3 vs 8; $P = .03$) and the group sequential trial design, which is prone to type I errors, are potential explanations. The same study design produced an apparent mortality benefit of corticosteroids in persistent ARDS[26] subsequently not reproduced in a larger, conventional randomized controlled trial.[27] More pertinently, the study by Torres et al[28] (discussed later) adopted a very similar patient group yet found no significant difference in mortality and nothing comparable to the effect reported by Confalonieri et al.[23]

Because the majority of studies addressing the use of corticosteroids in CAP are small and therefore underpowered, the use of meta-analysis is the most appropriate way to search for an outcome signal. Indeed, eight of the nine studies included in most of the meta-analyses, including the Cochrane meta-analysis,[12] reported a numerically higher survival in the corticosteroid-treated patients with severe CAP. The only study that did not report a numerically lower mortality with corticosteroid treatment ("severe" CAP defined post hoc) was the study by Blum et al.[29] However, among the patients defined as "severe" in this analysis, the mortality in the placebo group was only 7%, indicative of a nonsevere population in which corticosteroids would not be expected to provide benefit.

As described earlier, however, several of the included studies have methodologic flaws and evidence of allocation imbalance, and grouping them in a meta-analysis does not magically remove their shortcomings. This does not necessarily mean the conclusions of the

meta-analyses are wrong; it means simply that the strength of any conclusions drawn from the data we have must be considered exceedingly weak, far below the level that should be required to drive a change in clinical practice.

Even without a mortality benefit, an improvement in other clinical outcomes may be very beneficial from a patient or economic viewpoint. If we look at the other studies, what have they shown of clinical relevance? The largest and most methodologically rigorous study in severe CAP was conducted by Torres et al.[28] This multicenter trial included patients with severe CAP according to the 2007 ATS criteria[22] and a high inflammatory response as defined by a C-reactive protein level > 150 mg/L. A total of 120 patients were randomized in the study (61, steroid; 59, placebo). The primary outcome was treatment failure, defined according to a collection of outcomes, and was less common in the steroid group than in the placebo group (hazard ratio, 0.34; 95% CI, 0.14-0.87). However, the treatment failure outcome was driven almost entirely by patients in the steroid group having chest radiography between 72 and 120 hours' postadmission that showed less progression from baseline. The clinical relevance of better-looking chest radiographs when there was no difference in mortality, septic shock, organ failure, time to clinical stability, or length of stay is unclear.

To summarize all the remaining studies, the only positive clinically important results are that steroids have been associated with a reduced duration of antibiotic therapy[30] and a reduced length of hospital stay in the steroid group.[29,31] Analysis of these studies, however, shows that length of hospital admission was > 7 days, several days longer than would be expected in the United States or Australia, again raising the question of relevance. Faster normalization of temperature is frequently reported[29,30,32,33]; this finding is not surprising given the antipyretic effect of steroids, which also explains small improvements in time to clinical stability.

On the positive side for corticosteroids, a recent retrospective analysis of 758 patients with CAP found that patients treated with systemic corticosteroids (32%) seemed to have a lower risk of myocardial infarction during their inpatient stay (0.42 vs 0.89 event per 100 person-days).[34] Existing prospective randomized studies have not addressed this end point. Effective prevention of acute myocardial injury in patients with CAP is now an area of major concern and limited data, with only one small randomized trial of aspirin 300 mg/d for 1 month showing benefit[35] and a larger randomized trial of aspirin 100 mg/d showing no benefit.[36] If corticosteroids did have a benefit in this area, it would be significant clinically, but this topic needs proper study of the risks and benefits.

As for adverse events in these trials, only Snijders et al[32] reported more clinical failures in the steroid group, especially those with pneumococcal disease. It is interesting that a subsequent analysis of one of the studies that found an improvement in time to clinical stability with steroids[29] also reported that this benefit was not seen in patients with pneumococcal disease.[37] The only other significant side effect that reportedly occurred in most studies was hyperglycemia, which although not associated with adverse outcomes in these small studies, is known to be associated with worse outcomes in larger studies of sepsis.[38]

There are three significant concerns with respect to other potential adverse effects of steroids. First, there is a reasonable amount of observational data suggesting that steroid use in the setting of influenza may be associated with significantly greater mortality.[39] A recent analysis of patients from the Veterans Affairs system using propensity scoring to adjust for confounders also concluded that administration of corticosteroids was associated with a much higher mortality in patients with severe pneumonia due to influenza.[40] Second, there is evidence that even a short duration of steroid therapy is associated with significant complications in the following 90 days, including higher rates of sepsis, pulmonary emboli, and fractures.[41] Although not specific to pneumonia, these data underline the point that steroids are not benign drugs; to show the adverse impact, however, larger studies with longer periods of follow-up are needed.[42] Third, there is general concern about hyperglycemia, seen in several of the trials, and its known correlation with poorer outcomes in sepsis.

In summary, it is possible that corticosteroid therapy might be of benefit in a small subset of patients with severe CAP, but at present this group has not been defined, and even severe CAP was defined variably in the relevant studies. Proper benefit-risk analysis will require longer term follow-up than performed in most of the relevant studies, as well as evaluation of potential corticosteroid-related complications; we have yet to see studies designed to do this. Additional data are expected from the Veterans Affairs Extended Steroids in CAP trial, but the results have not yet been published, despite

enrollment being completed nearly 3 years ago. What is very clear is that use of corticosteroids outside of those with disease severe enough to require intensive care is clearly not supported by any published data, and the risk of harm from doing so is not insignificant. Of course, patients with CAP who have validated indications for corticosteroid use, such as acute exacerbation of COPD, should receive them. However, clinicians who have been convinced to routinely use corticosteroids in CAP need to re-evaluate their practice.

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