Corticosteroids in the treatment of community-acquired pneumonia: an evidence summary

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KEY WORDS
- glucocorticoids
- immunotherapy
- lower respiratory tract infection
- pneumonia, steroids

ABSTRACT
A strong inflammatory response to community-acquired pneumonia (CAP) is associated with excess morbidity and mortality. There is a growing interest in corticosteroids as an adjunctive treatment for patients hospitalized with CAP. We review recent randomized trials addressing the use of corticosteroids across the full range of CAP patients. Thirteen randomized controlled trials including 2005 patients have addressed the effect of short-term (single dose to 10 days) corticosteroid administration in patients with CAP. The results consistently show a shorter time to clinical stability and a shorter length of hospital stay on the order of 1 day. Some studies have also suggested a possible reduction in mortality. Adverse effects, primarily hyperglycemia and neuropsychiatric symptoms, are uncommon and neither serious nor prolonged. The results indicate a possibility that steroid administration should become a standard of care for patients with CAP.

Introduction
Community-acquired pneumonia (CAP) is the leading cause of infectious death in developed countries,1 and lower respiratory infections are the second leading cause of life-years lost globally.2 CAP is associated with billions of Euros in health care costs annually.1,3 Among hospitalized patients with CAP, mortality rates have remained high5 despite advances in antibiotic therapy6 and supportive care.6,7

CAP occurs when bacterial pathogens overcome the innate immune defences of the lower respiratory tract.3 There is a subsequent intense and prolonged inflammatory response.10 Although the local and systemic inflammatory responses may be necessary to clear the infection, they can also cause harm. The degree and duration of the inflammatory response are inversely associated with poor outcomes.10 Inflammation can worsen alveolar gas exchange, and in severe cases, leads to acute respiratory distress syndrome (ARDS).11,12 The most common cause of ARDS is pneumonia.13 Severe inflammation also contributes to septic shock and end-organ dysfunction.11,14

There has been considerable interest in immunomodulating agents, including corticosteroids, in the treatment of infections. For example, corticosteroids improve outcomes in Pneumocystis jiroveci pneumonia15 and bacterial meningitis.16 The first randomized trial of corticosteroids in CAP was published in 1956,17 and since then, there have been a number of other randomized trials.18-29 Two recent randomized trials28,29 add new knowledge to this long-standing discussion. This review places these recent findings into context of the broader literature to help clinicians answer the question: should adjunctive corticosteroids be used in the treatment of CAP?

Early randomized trials
The first randomized trial to evaluate corticosteroid therapy for CAP included 113 patients with culture-proven pneumococcal pneumonia treated with penicillin.17 The authors reported a shorter time to resolution of fever and subjective resolution of symptoms without any notable adverse effects. Two other trials were published in the following decades, showing a faster resolution of fever, but otherwise equivocal results.18,19

In 2005, a trial by Confalonieri et al.20 was the first to report a significant mortality benefit with corticosteroids. The Italian study randomized 46 patients with severe CAP in an intensive care unit...
to a 10-day hydrocortisone intravenous infusion or placebo. The trial was stopped early for benefit when eight (38%) of 23 patients died in the placebo group compared to none in the hydrocortisone group (P = 0.001). The Italian trial almost certainly overestimated the effect size: the mortality rate was higher than expected in the placebo group, and the trial was stopped early for benefit without predefined stopping criteria.20,31 Nonetheless, the successful trial encouraged other studies.21,29,31,34 with most showing benefits (Table 1).

Meta-analyses prior to the most recent trials Meta-analyses of corticosteroids for CAP have reported varying findings, some suggesting a mortality benefit in those with severe CAP.35,36 with low-dose corticosteroids,7 or with prolonged administration.36 No studies found a significant mortality benefit across all patients with CAP.28,41 A Cochrane review including patients with diverse types of pneumonia (eg, including Mycoplasma pneumoniae pneumonia) found low-quality evidence that corticosteroids reduced the time to symptom resolution and decreased the rate of relapsed disease.28 However, most of the clinical trials included in previous meta-analyses were small, enrolling less than 100 patients (Table 1). Two recent trials have further informed the discussion.28,29

Recent randomized trials Blum et al.28 randomized 785 patients hospitalized with CAP of varying severity to 50 mg of prednisone or placebo for 7 days. The primary outcome was time to clinical stability, defined as 24 hours after all vital signs normalized, including arterial oxygenation and mental status. The trial showed a convincing impact on the primary endpoint, reducing the median time to clinical stability by over 1 day from 4.4 (interquartile range, 4.0–5.0) days in the placebo group to 3.0 (interquartile range, 2.5–3.4) days in the prednisone group (hazard ratio [HR], 1.33; 95% confidence interval [CI], 1.15–1.50). There was a corresponding decrease in a median length of hospital stay by 1 day (7 vs 6 days, P = 0.012) and a suggestion of a possible reduction in pneumonia-associated complications (6% vs 3%, P = 0.056).

In-hospital hyperglycemia requiring new insulin therapy was more common in the intervention arm (19% vs 11%, P = 0.001), but there was no convincing difference in other adverse events including new insulin dependence at day 30 (1.3% in the prednisone group vs 0.3% in the placebo group, P = 0.12) or in intensive care admission, readmission, or mortality.

The findings of the trial are credible: it was well designed and executed, with low probability of bias. The finding of more rapid symptom resolution17,20,22,24 and shorter length of hospital stay20,21,25,27 is consistent with previous trials.

The second recent trial randomized 120 patients hospitalized with severe CAP and a serum C-reactive protein (CRP) greater than 150 mg/L (950 mmol/L) to methylprednisolone 0.5 mg/kg or placebo every 12 hours.28 The primary outcome was treatment failure, which was defined as a composite of septic shock, need for invasive mechanical ventilation, and death within 5 days or a ≥50% increase in radiographic pulmonary infiltrates or persistence of severe respiratory failure between days 3 and 5.

This trial also showed an apparent benefit in the primary outcome: 31% of patients had a treatment failure with placebo compared with 13% with methylprednisolone (P = 0.02). The results were driven by treatment failures occurring after 3 days (25% vs 3%, P = 0.001), because of a decrease in radiographic progression of disease (15% vs 2%, P = 0.007). Persistent respiratory failure, the need for mechanical ventilation, and septic shock were all less frequent in the methylprednisolone group, though none of these outcomes in themselves reached statistical significance.

The small sample size and very large effect driven by an outcome that is not important to patients limits inferences from this latest study. The suggestion of positive effects of corticosteroids is, however, consistent with all previous studies.

Should corticosteroids be restricted to patients with severe community-acquired pneumonia? The mortality benefit of corticosteroids remains uncertain, and if it does exist, it may be restricted to patients with severe CAP.28,35,36 This suggests that the most compelling indication for corticosteroid use may be in patients with more severe CAP.

Regardless of whether there is a mortality benefit from the use of corticosteroids in CAP—and whether it is restricted to the more severe patients—results convincingly demonstrate a reduction in time to symptom resolution/clinical stability and reduced length of stay in patients across the broad range of patients with CAP. An exploratory analysis in the largest trial failed to identify a difference in effect in those with higher versus lower disease severity.28

A reduction in hospital stay by 1 day would lead to considerable cost savings given that the median cost of hospitalization for CAP is €1200 to €6900 in Europe.42,43 The 1-day reduction is very similar to that demonstrated in patients with exacerbations of chronic obstructive pulmonary disease44 and corticosteroid use is well accepted and used broadly for this condition.46

Adverse effects of corticosteroids Corticosteroids have been used for decades and their adverse effects are well known. Short-term use is associated with hyperglycemia, which is typically transient.38,45 Neuropsychiatric side effects, which range from insomnia and irritability to mania, psychosis, and delirium, also occur.57 Gastrointestinal bleeding and secondary infections, other commonly cited adverse effects, do not appear to be increased with short-term use.45
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Location</th>
<th>No. of patients</th>
<th>Patient population</th>
<th>Follow-up time</th>
<th>Corticosteroid regimen</th>
<th>Notable outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wagner, 1956</td>
<td>USA</td>
<td>113</td>
<td>patients with pneumococcal pneumonia admitted to a general ward</td>
<td>NR, likely in-hospital</td>
<td>hydrocortisone oral every 6 hours 80-10 mg tapering dose over 5 days</td>
<td>faster resolution of fever faster resolution of subjective pneumonia symptoms</td>
</tr>
<tr>
<td>McHardy, 1972</td>
<td>Scotland</td>
<td>126</td>
<td>patients admitted to a respiratory ward with CAP</td>
<td>NR, likely in-hospital</td>
<td>prednisolone 5 mg every 6 hours orally for 7 days</td>
<td>no significant difference in time to resolution of fever, antibiotic duration, or mortality</td>
</tr>
<tr>
<td>Marik, 1993</td>
<td>South Africa</td>
<td>30</td>
<td>severe CAP in an ICU setting</td>
<td>to discharge from ICU</td>
<td>hydrocortisone 10 mg/kg IV 30 minutes prior to antibiotics</td>
<td>no significant difference in clinical outcomes</td>
</tr>
<tr>
<td>Confalonieri, 2005</td>
<td>Italy</td>
<td>46</td>
<td>severe CAP in an ICU or intermediate unit</td>
<td>60 days</td>
<td>hydrocortisone 200 mg IV bolus followed by 10 mg/hour IV for 10 days</td>
<td>lower 60 day mortality (0% vs 38%, P = 0.001) shorter hospital stay (21 vs 13 days, P = 0.03) shorter duration of mechanical ventilation (10 vs 4 days, P = 0.007) faster improvements in serum CRP (P = 0.01) and PaO2:FiO2 (P &lt;0.0001).</td>
</tr>
<tr>
<td>El-Ghamrawy, 2006</td>
<td>Saudi Arabia</td>
<td>34</td>
<td>severe CAP in ICU</td>
<td>in-hospital</td>
<td>hydrocortisone 200 mg IV bolus followed by 10 mg/hour IV for 7 days</td>
<td>lower APACHE II score at day 8 (P &lt;0.05) shorter length of hospital stay (23 vs 16 days, P &lt;0.001) shorter duration of mechanical ventilation (11 vs 6 days, P &lt;0.001) no significant difference in in-hospital mortality (35% vs 18%, P &gt;0.05).</td>
</tr>
<tr>
<td>Mikami, 2007</td>
<td>Japan</td>
<td>31</td>
<td>all patients hospitalized with CAP</td>
<td>in-hospital</td>
<td>prednisolone 40 mg IV daily for 3 days</td>
<td>no significant difference in hospital stay (16 vs 11 days, P = 0.18) faster normalization in basal temperature and respiratory rate (P = 0.015, P = 0.008)</td>
</tr>
<tr>
<td>Snijders, 2010</td>
<td>Netherlands</td>
<td>213</td>
<td>all patients hospitalized with CAP</td>
<td>30 days</td>
<td>prednisolone 40 mg IV or orally for 7 days</td>
<td>late failureb more common (9% vs 19%, P = 0.04) no significant difference in clinical cure at day 30 (77% vs 66%, P = 0.08) no significant difference in time-to-clinical stability or length of stay (P = 0.97 and P = 0.16) no significant difference in mortality (6% vs 6%, P = 0.93)</td>
</tr>
<tr>
<td>Fernández-Serrano, 2011</td>
<td>Spain</td>
<td>45</td>
<td>severe CAP with extensive consolidations or respiratory failure</td>
<td>1 month</td>
<td>methylprednisolone 200 mg IV bolus, followed by tapering infusion (3.3 to 0.8 mg IV/hour) over 9 days</td>
<td>faster time to &quot;resolution of morbidity&quot;c (7 vs 5 days, P = 0.02) improved PaO2:FiO2 (P = 0.001) no significant difference in need for mechanical ventilation (23% vs 4%, not significant)</td>
</tr>
</tbody>
</table>
Patients with higher risks of severe hyperglycemia (eg, those with fragile diabetes) or neuropsychiatric side effects (eg, patients with a history of corticosteroid-induced neuropsychiatric complications) might prefer to avoid the risk of these side effects. Given the relatively infrequent and transient nature of the adverse effects, it is likely that most informed patients would choose an intervention that reduces their stay in hospital by a day.

Dosing The randomized trials have tested a variety of corticosteroid agents, doses, and durations, leaving the optimal dose and duration uncertain. Most trials, however, used 3 to 7 days of moderate dose corticosteroids (approximately 0.5–1 mg/kg of prednisone-equivalent per 24 hours).

Conclusions Adjunctive corticosteroids for treatment of CAP reduce the duration of symptoms and hospitalization by approximately 1 day. There may also be a mortality benefit, which may be restricted to those with more severe disease, although this is less certain. If there is any impact on mortality, it is a reduction. These results suggest the possibility that routine use of corticosteroids in patients with CAP should become a standard of care.

REFERENCES


Glikokortykosteroidy w leczeniu pozaszpitalnego zapalenia płuc – podsumowanie danych naukowych

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**STRESZCZENIE**

U chorych na pozaszpitalne zapalenie płuc (PZP) silna odpowiedź zapalna spowodowana przez chorobę wiąże się ze zwiększeniem chorobowości i ryzyka zgonu. Rośnie zainteresowanie zastosowaniem kortykosteroidów jako dodatkowego leczenia u chorych hospitalizowanych z powodu PZP. W niniejszym artykule omawiamy najnowsze badania z randomizacją, w których oceniano zastosowanie kortykosteroidów u chorych na PZP we wszystkich stadiach ciężkości. Wpływ krótkotrwałego (pojedyncza dawka – 10 dni leczenia) stosowania kortykosteroidów u chorych na PZP oceniano w 13 badaniach z randomizacją, w których wzięło udział 2005 chorych. Wyniki jednoznacznie wskazują na skrócenie czasu do osiągnięcia stabilności klinicznej i skrócenie o 1 dzień czasu hospitalizacji. Wyniki niektórych badań sugerują również, że kortykosteroidy mogą zmniejszać ryzyko zgonu. Skutki niepożądane, głównie hiperglykemia i objawy neuropsychiatryczne, występują rzadko i nie są ani poważne, ani długotrwałe. Wyniki te wskazują, że należy rozważyć stosowanie steroidów w ramach rutynowego leczenia chorych na PZP.

**SŁOWA KLUCZOWE**

glikokortykosteroidy, immunoterapia, infekcja dolnych dróg oddechowych, sterydy, zapalenie płuc