Commentary

Adjuvant corticosteroids for patients hospitalized with community-acquired pneumonia: is it time?

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Community-acquired pneumonia (CAP) is one of the most common infectious diseases leading to hospital admission, and the third-leading cause of death worldwide (1,2). Despite the availability of antibacterial treatment active *in vitro* for most recognized causes of bacterial CAP, this common disease still carries a significant burden of morbidity and mortality (3). Hence, efforts to develop adjunct therapeutic interventions for CAP have been intensified over the last decades. Of those, corticosteroid therapy is the most promising, with significant clinical benefits demonstrated in various randomized controlled trials (4-8). However, the use of corticosteroids in patients with CAP has not been clearly recommended thus far, neither in the main guidelines for CAP (9,10), nor in state-of-the-art review papers (1-3,11). Even the editorials that came out with randomized trials demonstrating positive impact of corticosteroids on clinical outcomes were rather cautious, and basically recommended additional studies before corticosteroids be recommended for CAP (12,13), with the notable exception of one (14).

The recent publication in the *Annals of Internal Medicine* of an updated systematic review and meta-analysis on randomized trials of systemic corticosteroids in adults hospitalized because of CAP was remarkable by the observation that adjuvant corticosteroids may be associated with reduction in all-cause mortality (15). Indeed, based on the analysis of 12 randomized trials, totalling 1,974 patients, the risk ratio (RR) for death was 0.67 (95% CI, 0.45–1.01) with the use of different regimens of corticosteroids (*Table 1*). All-cause mortality was 7.9% (79/997) in the placebo groups *vs.* 5.3% (52/977) in the corticosteroid groups, which translates into a risk difference for death of 2.8%. Other findings from this meta-analysis support the plausibility of the beneficial effects of corticosteroids in patients admitted for CAP: (I) the effect seems to increase with the severity of CAP, with a significant mortality benefit observed in trials that met pre-specified criteria for severe CAP (i.e., when at least 70% of patients enrolled had severe CAP at baseline, and/or when mortality was at least 15% in the control group), but not in trials that enrolled less severe CAP (15); (II) adjuvant corticosteroids were also associated with reductions in the need for mechanical ventilation (RR =0.45; 95% CI, 0.26–0.79), with an estimated number needed to treat of approximately 20 to avoid one requirement for mechanical ventilation, the development of acute respiratory distress syndrome (RR =0.24; 95% CI, 0.10–0.56), the time to clinical stability (mean difference, −1.22 days; 95% CI, −2.08 to −0.35 days), and the duration of hospitalization (mean difference, −1.00 days; 95% CI, −1.79 to −0.21 days); (III) these benefits were observed at a reasonable cost: a moderate increased in the frequency of hyperglycemia requiring treatment (RR =1.49; 95% CI, 1.01–2.19), but no excess of gastrointestinal haemorrhage (15). Of note, most trials did not observe any signal of an increased risk of infectious complications, which suggests, as was inferred from animal studies (21), that a short course (<7 days) of corticosteroids has probably no deleterious effect on the control of bacterial CAP, provided an adequate antibacterial treatment is administered concomitantly.

Table 1 Adjuvant corticosteroid regimens evaluated in the randomized controlled trials included in the meta-analysis

Corticosteroid agent	Route, dose, and duration	References
Prednisone	Oral, 50 mg/day, 7 days	(4)
Prednisolone	Oral, 5 mg every 6 h, 7 days	(16)
	Oral or intravenous, 40 mg/day, 7 days	(7)
	Intravenous, 40 mg/day, 3 days	(17)
Hydrocortisone	Intravenous, 200 mg bolus followed by 10 mg/h, 7 days	(5)
	Intravenous, 200 mg bolus followed by 12.5 mg/h, 7 days	
	Intravenous, 10 mg/kg 30 min before antibiotics start	(18)
	Oral, 80–100 mg every 6 h followed by tapering doses, 5 days	(19)
Methylprednisolone	Intravenous, 200 mg bolus followed by tapering infusions, 9 days	(20)
	Intravenous, 0.5 mg/kg every 12 h, 5 days	(8)
Dexamethasone	Intravenous, 5 mg/day, 4 days	(6)

Two considerations must however be kept in mind: firstly, Snijders *et al.* found an increased risk of CAP recurrence in the group of patients who received adjuvant corticosteroids (20/104, 19%), as compared to placebo (10/109, 9%), which suggests that corticosteroids may exert a deleterious effect on immune system, and/or may trigger a rebound effect after their discontinuation (7). Secondly, evidence available to date suggests that for severe CAP related to influenza, corticosteroids may be harmful (22,23). Hence, the use of adjuvant corticosteroids should probably be discouraged in patients with severe CAP when influenza is in the differential, at least until this diagnosis has been ruled out.

Going back to the survival benefit associated with adjuvant corticosteroids according to the recent meta-analysis, why don't we all take into account these data collected from randomized controlled trials, observed with a cheap and commonly available therapeutic intervention—adjuvant corticosteroids—for a quite common disease? The answers are not straightforward, and we must acknowledge that our cautiousness may well be wrong: if the survival benefits associated with adjuvant corticosteroids is definitely demonstrated in a couple of years from now, it would mean that lives could have been saved by an earlier and broader implementation of this therapeutic intervention, as suggested by more optimistic editorials (14). The main reasons behind our reluctance to pass the boarder, and recommend systemic adjuvant corticosteroids for all patients admitted with CAP, are as follows:

(I) Differences between patients in the real life, and in randomized clinical trials, must be considered: Most of these trials excluded patients at higher risk of corticosteroids-related adverse events, including gastrointestinal bleeding within the past 3 months (4,5,8), severe immunosuppression (4-8), nosocomial pneumonia (4-8), pregnancy (4-8), and uncontrolled diabetes mellitus (8). The risk-benefit ratio of adjuvant corticosteroids in these populations may be detrimental, so that they should probably not be considered as relevant candidates for this intervention, pending additional data. Along the same line, it must be outlined that data on the use of adjuvant corticosteroids for CAP in the outpatient setting are scarce: a recent study in children with CAP who were not admitted (24), suggests that it may even be deleterious. Hence, adjuvant corticosteroid in patients with CAP who are not admitted should be discouraged, pending additional data.

(II) As remarkably pointed out by G. Waterer in an editorial paper recently published in the *Journal of Thoracic Disease* (13), one randomized trial included in the meta-analysis is obviously an outlier, as reflected by the Forrest plot in Figure 1 (15). This outlier was a study on severe CAP, admitted in intensive care units, that was suspended after an interim analysis of data from the first 46 patients, found a 60-day mortality of 38% in the placebo group (8/21), as compared to 0% (0/23) in the corticosteroid group (P=0.009), in which patients received low-dose, continuous infusion of hydrocortisone during 7 days (5). Whatever the reasons behind the dramatic differences in survival observed within this trial conducted 15 years ago

[2000–2003], this has not been replicated in any other randomized trials since: the impact on survival was either non-significant, or mildly positive, but never came close to those optimistic findings. It must be outlined that, if this study had been excluded from the meta-analysis due to its 'outlier' status, then the overall conclusion of the meta-analysis would have been changed to 'minimal or no benefit' of adjuvant corticosteroids on mortality in patients admitted for CAP.

(III) Although meta-analysis are, by essence, obtained by merging different trials performed in different settings, this meta-analysis is remarkable by the striking heterogeneity of the interventions evaluated: Indeed, the studies included in this meta-analysis evaluated a variety of corticosteroid agents, with different doses, route of administration, and duration (*Table 1*). This is a significant limitation to the implementation of the findings from this meta-analysis, as the choice of the corticosteroid regimen would not be straightforward, although those evaluated in the largest and most recent studies should probably be prioritized: oral prednisone, 50 mg daily during 7 days (5), or intravenous methylprednisolone, 0.5 mg/kg per 12 h during 5 days (8). Likewise, the optimal timing of corticosteroids in relation to antibacterial treatment initiation remains undefined.

Although this is our duty, as clinicians, to offer the best care for our patients, this is equally our role to analyse carefully, and with criticism, the data provided by randomized trials, and meta-analysis. Data available thus far strongly suggest that adjuvant systemic corticosteroids may be of benefit for a significant proportion of patients admitted with CAP, but the population that will most benefit, and the interventions that will have the best effect, remain to be determined. It is conceivable that, among the large group of patients admitted for CAP, adjuvant corticosteroids are beneficial in a subgroup (e.g., as suggested by the meta-analysis, patients with severe CAP), and deleterious in others. This was the rationale behind Torres *et al.* randomized trial, where they hypothesized that adjuvant corticosteroids would most likely be beneficial in patients with severe CAP, and a strong inflammatory response. Hence, they only enrolled patients with severe CAP, and a plasma level of C-reactive protein >150 mg/L at admission, and found a significant reduction of treatment failure in patients treated with adjuvant corticosteroids (8). Unfortunately, the largest randomized controlled trial performed thus far could not identify any effect modification in different pre-specified subgroups, despite an enrolment of almost 800 patients admitted for CAP (4).

Given all the considerations presented above, this is our opinion that adjuvant corticosteroids are probably beneficial in a substantial proportion of patients admitted for CAP, including for survival. However, at least one additional large-scale randomized controlled trial, stratified on selected populations, is still necessary, before adjuvant corticosteroid therapy be safely recommended in the guidelines for the management of CAP, for the population most likely to benefit.

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Footnote

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References

1. Musher DM, Thorner AR. Community-acquired pneumonia. N Engl J Med 2014;371:1619-28.
2. File TM. Community-acquired pneumonia. Lancet 2003;362:1991-2001.
3. Wunderink RG, Waterer GW. Clinical practice. Community-acquired pneumonia. N Engl J Med 2014;370:543-51.
4. Blum CA, Nigro N, Briel M, et al. Adjunct prednisone therapy for patients with community-acquired pneumonia: a multicentre, double-blind, randomised, placebo-controlled trial. Lancet 2015;385:1511-8.
5. Confalonieri M, Urbino R, Potena A, et al. Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study. Am J Respir Crit Care Med 2005;171:242-8.
6. Meijvis SC, Hardeman H, Remmelts HH, et al. Dexamethasone and length of hospital stay in patients with community-acquired pneumonia: a randomised, double-blind, placebo-controlled trial. Lancet 2011;377:2023-30.

7. Snijders D, Daniels JM, de Graaff CS, et al. Efficacy of corticosteroids in community-acquired pneumonia: a randomized double-blinded clinical trial. Am J Respir Crit Care Med 2010;181:975-82.
8. Torres A, Sibila O, Ferrer M, et al. Effect of corticosteroids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response: a randomized clinical trial. JAMA 2015;313:677-86.
9. Woodhead M, Blasi F, Ewig S, et al. Guidelines for the management of adult lower respiratory tract infections--full version. Clin Microbiol Infect 2011;17 Suppl 6:E1-59.
10. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007;44 Suppl 2:S27-72.
11. Waterer GW, Rello J, Wunderink RG. Management of community-acquired pneumonia in adults. Am J Respir Crit Care Med 2011;183:157-64.
12. Wunderink RG. Corticosteroids for severe community-acquired pneumonia: not for everyone. JAMA 2015;313:673-4.
13. Waterer G. Systemic corticosteroids and community-acquired pneumonia-cautious optimism or wishful thinking? J Thorac Dis 2015;7:E622-4.
14. Annane D. Corticosteroids and pneumonia: time to change practice. Lancet 2015;385:1484-5.
15. Siemieniuk RA, Meade MO, Alonso-Coello P, et al. Corticosteroid therapy for patients hospitalized with community-acquired pneumonia: a systematic review and meta-analysis. Ann Intern Med 2015;163:519-28.
16. McHardy VU, Schonell ME. Ampicillin dosage and use of prednisolone in treatment of pneumonia: co-operative controlled trial. Br Med J 1972;4:569-73.
17. Mikami K, Suzuki M, Kitagawa H, et al. Efficacy of corticosteroids in the treatment of community-acquired pneumonia requiring hospitalization. Lung 2007;185:249-55.
18. Marik P, Kraus P, Sribante J, et al. Hydrocortisone and tumor necrosis factor in severe community-acquired pneumonia. A randomized controlled study. Chest 1993;104:389-92.
19. Wagner HN Jr, Bennett IL Jr, Lasagna L, et al. The effect of hydrocortisone upon the course of pneumococcal pneumonia treated with penicillin. Bull Johns Hopkins Hosp 1956;98:197-215.
20. Fernández-Serrano S, Dorca J, Garcia-Vidal C, et al. Effect of corticosteroids on the clinical course of community-acquired pneumonia: a randomized controlled trial. Crit Care 2011;15:R96.
21. Sibila O, Luna CM, Agustí C, et al. Effects of glucocorticoids in ventilated piglets with severe pneumonia. Eur Respir J 2008;32:1037-46.
22. Martin-Loeches I, Lisboa T, Rhodes A, et al. Use of early corticosteroid therapy on ICU admission in patients affected by severe pandemic (H1N1)v influenza A infection. Intensive Care Med 2011;37:272-83.
23. Brun-Buisson C, Richard JC, Mercat A, et al. Early corticosteroids in severe influenza A/H1N1 pneumonia and acute respiratory distress syndrome. Am J Respir Crit Care Med 2011;183:1200-6.
24. Ambroggio L, Test M, Metlay JP, et al. Adjunct Systemic Corticosteroid Therapy in Children With Community-Acquired Pneumonia in the Outpatient Setting. J Pediatric Infect Dis Soc 2015;4:21-7.

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