Intern Emerg Med (2015) 10:629–630
DOI 10.1007/s11739-015-1247-z

THE CUTTING EDGE: RESEARCH UPDATE

Adjunct prednisone therapy for patients with community-acquired pneumonia

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Received: 8 April 2015 / Accepted: 15 April 2015 / Published online: 22 May 2015

Background

Pneumonia is one of the principal causes of morbidity and mortality worldwide, despite the advances in antibiotic therapies and in preventive measures [1]. The intense inflammatory response that was of fundamental importance in the pre-antibiotics era nowadays might be excessive. In fact, it can lead to multiple organ failure, thus causing more harm than benefit [2]. Corticosteroids have a strong anti-inflammatory effect; therefore, their use in pneumonia has been studied for a long time. One of the most important trials was recently published by Meijvis [3]. A 4-day course of 5 mg of dexamethasone was compared to placebo, showing a 1-day reduction in hospital stay, but no difference in mortality. A meta-analysis by Nie [4] does not find any significant reduction in pneumonia overall mortality; however, a subgroup analysis shows a significant reduction in mortality in both studies considering patients with severe pneumonias and treating subjects for more than 5 days. Therefore, the authors conclude that adequately powered double-blind randomized controlled trials (RCTs) are warranted to give recommendations for the use of steroids in pneumonia.

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Summary

The investigator-initiated, multicenter, double-blind, randomized, placebo-controlled trial by Blum et al. [5] compared the use of short-term prednisone versus placebo in patients admitted to hospital for community-acquired pneumonia (CAP). Patients were considered eligible if they were 18 years of age or older, and if they had community-acquired pneumonia, as defined by a new infiltrate on chest radiograph with the presence of at least one among acute respiratory signs and symptoms (cough, sputum production, dyspnea), core body temperature ≥38 °C, auscultatory findings of abnormal breathing sounds or rales, leucocyte count higher than 10000/μL or less than 4000/μL. The main exclusion criteria were: gastrointestinal bleeding within the past 3 months, a condition requiring more than 0.5 mg/kg per day prednisone equivalent and severe immunosuppression. The study was designed to test the hypothesis that corticosteroids would reduce time to clinical stability in patients with community-acquired pneumonia without relevant adverse effects with a 85 % power, assuming a 25 % reduction in the risk of non-stability after 7 days (from 33 to 25 % in the prednisone group). Secondary endpoints were, among the others, time to effective discharge from hospital, incidence of complications due to community-acquired pneumonia, corticosteroids side effects, recurrence of pneumonia, re-admission to hospital, all-cause mortality.

The primary endpoint was time to clinical stability, defined as days until stable vital signs for at least 24 h (including temperature of 37.8 °C or lower, heart rate ≤100 beats per min, spontaneous respiratory rate ≤24 breaths per min and adequate oxygenation on room air, systolic blood pressure ≥90 mmHg). Of 2911 consecutive patients presenting with CAP and assessed for eligibility,

the majority was excluded because of another indication for steroids (667) or severe immunosuppression (508). Only 785 were randomly assigned (in a 1:1 ratio) to receive either 50 mg of prednisone ($n = 392$) or placebo ($n = 393$) daily for 7 days, and analysed by intention-to-treat. Patients started antibiotic therapy as soon as CAP was confirmed. Structured follow-up telephone interviews for secondary outcomes after discharge were performed on day 30.

The median time to clinical stability was shorter in the prednisone group (3 days, IQR 2.5–3.4) than in the placebo group (4.4 days, 4.0–5.0; hazard ratio [HR] 1.33, 95 % CI 1.15–1.50, $p < 0{\cdot}0001$), even in the per-protocol analysis.

Pneumonia-associated complications until day 30 did not differ between groups (3 % in the prednisone group and 6 % in the placebo group; odds ratio [OR] 0.49 [95 % CI 0.23–1.02]; $p = 0.056$). Nevertheless, the prednisone group had a higher incidence of in-hospital hyperglycaemia needing insulin treatment (19 vs 11 %; OR 1.96, 95 % CI 1.31–2.93, $p = 0.0010$).

The authors conclude that 7-day prednisone treatment shortens time to clinical stability without an increase in complications in patients admitted to hospital with community-acquired pneumonia.

Strengths of the study

It is a well-conducted RCT, and it is the biggest so far on the use of steroids in community-acquired pneumonia.

Question marks

- The primary outcome of the study is time to clinical stability, based on the stability of vital signs. However, some of the clinical parameters considered (i.e. body temperature and blood pressure) might be altered by steroids even in the absence of a clinical improvement. We wonder if steroid therapy really contributes to a faster resolution of pneumonia, or if it only reduces the signs and symptoms of infection.
- This trial demonstrates a reduction in the time to clinical stability and in the days of hospitalization; however, there was no clear benefit on hard outcomes, such as mortality. On the other hand, the incidence of hyperglycemia needing insulin therapy was significantly increased by steroids. We wonder if a one-day reduction in hospitalization is worth the need of home insulin therapy.
- Most of the patients assessed for eligibility were excluded because of another indication for steroids or immunosuppression; the low rate of eligible patients might affect external validity.
- The authors did not report the type of pneumonia at the first chest X-ray (lobar versus interstitial). It would be interesting to know if different radiological patterns have a different response to steroid therapy.

Sponsorship

The Swiss National Foundation was the funder of the study. It had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study, and had final responsibility for the decision to submit for publication.

Clinical bottom line

Prednisone might be considered in the usual therapy of pneumonia to shorten the time to clinical stability. However, since steroids have never been shown to improve hard outcomes, their use cannot be routinely recommended. Clinicians should balance the benefit with the increased risk of hyperglycemia.

Conflict of interest The Authors declare that they have no conflict of interest.

Statement of human and animal rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with human and animals performed by any of the authors.

Informed consent None.

References

1. WHO (2014) The top 10 causes of death. World Health Organization, Geneva
2. Dellinger RP, Levy MM, Rhodes A et al (2013) Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med 39(2):165–228
3. Meijvis SCA, Hardeman H, Remmelts H et al (2011) Dexamethasone and length of hospital stay in patients with community-acquired pneumonia: a randomised, double-blind, placebo-controlled trial. Lancet 377:2023–2030
4. Nie W, Zhang Y, Cheng J, Xiu Q et al (2012) Corticosteroids in the treatment of community-acquired pneumonia in adults: a meta-analysis. PLoS One 7(10):e47926
5. Blum CA, Nigro N, Briel M et al (2015) Adjunct prednisone therapy for patients with community acquired pneumonia: a multicentre, double-blind, randomised, placebo-controlled trial. Lancet. doi:10.1016/S0140-6736(14)62447-8