

Glucocorticoids Use in CAP: The Good, The Bad and The Ugly!

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Despite advances in antibiotic therapy and mechanical ventilation, inpatient mortality in community acquired pneumonia remains alarmingly high (8-11%) [1,2]. The idea of using glucocorticoids in patients with community-acquired pneumonia (CAP) was first explored in 1950s [3]; to this date, despite multiple trials, the question still remains controversial – are glucocorticoids (GCS) beneficial in treatment of CAP?

The Good

Proponents of glucocorticoid use in CAP argue that several trials showed steroid use shortens time to clinical stability, time to hospital discharge and even decrease mortality at relatively low risk of side effects. The debate was propelled particularly by two randomized controlled trials published in 2015 [4,5] as well as three meta analyses with some favorable outcomes [6-8].

The first study by Blum, *et al.* [4] was a multi-center, randomized, double blind trial that included 800 patients with CAP of all classes of severity. Patients were randomly assigned to prednisone 50 mg daily for 7 days or placebo within 24h of presentation. The primary outcome of the study was defined as time to clinical stability (stable vital signs for 24h: Temperature < 37.8°C, HR < 100, RR < 24, SBP > 90 mmHg, PaO₂ ≥ 60 mm Hg or SpO₂ ≥ 90 on room air and normal mental status). Secondary outcomes included time to discharge, length of treatment, ICU admission and mortality. The study found significantly shorter median time to clinical stability in the prednisone group as compared to placebo (3.0 vs 4.4 days, HR 1.33, p < 0.0001) as well as shorter median time to effective discharge (6.0 vs 7.0 days, HR 1.19, p = 0.012) however, no difference in secondary outcomes or impact on mortality (p = 0.57).

The second study by Torres, *et al.* [5] studied a subgroup of patients with severe CAP and CRP > 15 mg/dL. Severe CAP was defined as pneumonia severity index (PSI) class V or by modified ATS criteria (major criteria: requirement of mechanical ventilation, presence of septic shock; minor criteria: systolic blood pressure < 90 mm Hg, multilobar involvement, PaO₂/FiO₂ < 250; 2-3 minor or 1 major criteria required to define as severe CAP) [9]. 120 patients were randomized to receive either an intravenous bolus of 0.5 mg/kg per 12 hours of methylprednisolone or placebo for 5 days, started within 36 hours of hospital admission. The primary outcome was rate of treatment failure. Early treatment failure was defined as clinical deterioration within 72 hours (development of shock, need for mechanical ventilation or death), and late treatment failure was defined as radiographic progression (increase by 50% in pulmonary infiltrates), respiratory failure, shock, and death between 72 and 120h. Secondary outcomes included length of stay, time to clinical stability and in-hospital mortality. The study found significantly higher incidence in late treatment failure (15 vs 2, p = 0.001) in the placebo group, mostly due to an increase in radiographic progression (p = 0.007) and to a lesser degree due to late appearance of septic shock (p = 0.06). No significant difference in early treatment failure, mortality or other secondary outcomes was found.

Out of the three large metaanalysis [6-8] published till date, two of them showed statistically significant mortality benefit in subgroup of patients with severe CAP [9]. Upon closer inspection, the significance of this finding was largely driven by a single small trial by Confalonieri [10] in 2005 which had several limitations (small size, differences in baseline characteristics of the two groups and early stop for benefit). All three meta-analyses although reported favorable outcomes for length of hospital stay and time to clinical stability. Length of stay as well as time to clinical stability were 1 day shorter in the steroid arm [6-8].

The Bad

Both abovementioned randomized controlled trials have several limitations. Neither of the studies was sufficiently powered to assess mortality and the choice of primary outcomes indeed raises questions. In the trial by Blum [4], the difference in time to clinical stability observed might be partly due to the effect of glucocorticoids on suppressing fever and therefore stabilization of other vital signs. In the trial by Torres [5], the difference between the steroid and placebo arm was mainly due to decreased rate of radiographic progression, the clinical significance of radiographic progression of pneumonia is doubtful, especially since no difference in other important outcomes such as length of stay, need for mechanical ventilation or death was observed.

Although the results from the existing meta-analysis appear to be in favor of GCS use, especially in severe CAP, several limitations exist. Adrenal function was not assessed in most RCTs. In addition, the doses and duration of GCS treatment were different among the studies, which contributed to a significant clinical heterogeneity in systematic evaluation. Also, no clear recommendations can be made regarding which steroids should be used and for how long. Most importantly neither study showed significant difference in mortality in non-severe CAP, and the mortality difference in severe CAP is still debatable.

The Ugly

On worst side, all three meta-analyses jointly report higher incidence of hyperglycemia requiring insulin [6-8] as the most common side effect. Chen, *et al.* [8] also describe higher incidence of gastrointestinal bleeding and super infection in the steroid group, however this was statistically not significant. In addition, most studies excluded patients who were at high risk of adverse effects from corticosteroids, which underestimates overall risk.

Conclusion

The idea of using glucocorticoids in CAP seems attractive, as excessive inflammation has been shown to play important role in poor outcomes in CAP, and glucocorticoids are efficient in decreasing detrimental inflammatory response in sepsis and meningitis. The summary of evidence shows that glucocorticoids shorten length of stay for about 1 day and may improve mortality in severe CAP. Despite the optimism of some studies, however, to recommend routine use of glucocorticoids seems premature, for three reasons. First, no clear mortality benefit has been observed in non-severe CAP and the mortality benefit in severe CAP is still questionable. Second, data on adverse effects might be underestimated as studies were insufficiently powered to observe significant difference. Third, before advocating use of GCS as new standard of care, the optimal dosing, type of steroids and length of treatment needs to be determined. Further large scale studies are required to answer the question precisely.

Bibliography

1. Sean B Smith, *et al.* "Trends in Pathogens Among Patients Hospitalized for Pneumonia from 1993 to 2011". *JAMA Internal Medicine* 174.11 (2014): 1837-1839.
2. Niederman MS. "Recent advances in community-acquired pneumonia: inpatient and outpatient". *Chest* 131.4 (2007): 1205-1215.
3. Wagner Hn Jr, *et al.* "The effect of hydrocortisone upon the course of pneumococcal pneumonia treated with penicillin". *The Johns Hopkins Medical Journal* 98.3 (1956): 197-215.
4. Blum CA, *et al.* "Adjunct prednisone therapy for patients with community-acquired pneumonia: a multicentre, double-blind, randomised, placebo-controlled trial". *Lancet* 385.9977 (2015): 1511-1518.
5. Torres A, *et al.* "Effect of glucocorticoids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response: a randomized clinical trial". *JAMA* 313.7 (2015): 677-686.
6. Reed A C, *et al.* "Corticosteroid Therapy for Patients Hospitalized With Community-Acquired Pneumonia: A Systematic Review and Meta-analysis". *Annals of Internal Medicine* 163.7 (2015): 519-528.

7. Horita N, *et al.* "Adjunctive Systemic Glucocorticoids for Hospitalized Community-Acquired Pneumonia: Systematic Review and Meta-Analysis 2015 Update". *Scientific Reports* 5 (2015): 14061.
8. Chen LP, *et al.* "Efficacy and safety of glucocorticoids in the treatment of community-acquired pneumonia: A meta-analysis of randomized controlled trials". *World Journal of Emergency Medicine* 6.3 (2015): 172-178.
9. Ewig S, *et al.* Severe community-acquired pneumonia: assessment of severity criteria. *Am J Respir Crit Care Med* 158.7 (1998):1102-1108.
10. Confalonieri M, *et al.* "Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study". *American Journal of Respiratory Critical Care Medicine* 171.3 (2005): 242-248.

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