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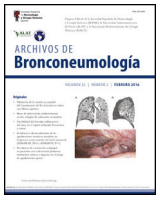

Editorial

Corticosteroids and Severe Community-acquired Pneumonia: New Data, New Questions and a Swinging Pendulum

The risks and benefits of corticosteroids in the setting of community-acquired pneumonia (CAP) have been controversial for over a decade. Early studies were generally either of poor quality with significant methodological problems or failed to demonstrate clinically significant benefits.[1] Given the deleterious effects of corticosteroids, especially higher risks of infection and hyperglycemia, recent guidelines for CAP recommended against their routine use noting that there may be a subset of patients who would benefit, but studies had so far failed to define this group.[2]

Two recently published multicenter, randomized, placebo-controlled trials in patients with severe CAP have substantially increased the quality of data available to make recommendations on corticosteroid treatment. Unfortunately, these studies have conflicting results that cannot be resolved by statistical techniques like meta-analysis, but instead require careful analysis of the individual studies, their results and the potential reasons behind the different findings.

In a randomized trial based in 42 Veterans Affairs Medical Centers in the United States, 586 patients with severe CAP requiring ICU admission were randomized to methylprednisolone (starting dose of 40 mg intravenous dose per day for 7 days with tapering over a total of 20 days) or placebo.[3] There was no significant difference in the primary outcome of 60-day mortality (16% vs. 18%, $p = 0.61$). Prespecified and post hoc analyses also failed to identify a subgroup of patients who benefitted from steroids.

In contrast, a randomized trial in 31 French centers, 800 patients with severe CAP requiring ICU admission were randomized to hydrocortisone (starting dose of 200 mg per day by continuous infusion for 4 days with tapering over a total of 8 or 14 days) or placebo.[4] While full enrolment was not achieved due to the COVID-19 pandemic, a planned interim analysis found a significant difference in the primary outcome of 28-day mortality favoring the hydrocortisone arm (6.3% vs. 11.9%). The mortality benefit persisted at the 90-day assessment point. Secondary outcomes including initiation of vasopressors and mechanical ventilation also favored the treatment arm.

Why did the US and French trials have such different results and how do we reconcile them with prior studies? There are three obvious differences between the two studies. Although the dose equivalence of steroids used in both studies is similar, there may be differences between hydrocortisone and methylprednisone that have not so far been demonstrated in pharmacological studies of relevance in the mechanism of benefit in severe CAP.

Gender differences in critical care are well recognized, including in community-acquired pneumonia, from which men are significantly more likely to die than women.[5] The US study in the VA system was 96% male, whereas the French study was 69% male and post hoc analysis showed the survival benefit of steroids appeared much stronger in females. Similarly, post hoc analyses suggested a significant difference in the impact of steroids on survival between men and women in the COVID-19 RECOVERY trial.[6] While post hoc analyses should always be interpreted with caution, gender-specific influences on the benefit and risk of steroids need to be considered in the powering and prespecified analyses of future trials.

The window of opportunity for steroids to impact positively on outcome may also be critical. The French trial administered steroids within 24 h of meeting eligibility criteria whereas the US trial allowed up to 96 h. The total duration of corticosteroid exposure also differed between the studies, 20 days by study protocol in the US study, and a median of five days in the French study. Shorter durations should help reduce the side effects of corticosteroids and if their primary effect is to reduce organ damage in the acute phase, longer durations may not be justified. Clearly, it will be vital to establish the therapeutic window for steroids in future trials.

One further potential difference relates to the microbiological etiology of CAP, with the efficacy of steroids potentially varying depending on the pathogen and resulting mechanisms of injury. Unlike the US study, the French study excluded patients with evidence of influenza infection due to observational studies suggesting increased mortality in patients with influenza receiving corticosteroid treatment.[7] Confusingly while in the French study while 70% of patient had an elevated c-reactive protein suggestive of bacterial infection, the largest benefit of steroids was seen in patients who did not have a definitive pathogen identified. A prior study showing a reduction in antibiotic use with steroids in patients with CAP also found this did not apply to patients with proven pneumococcal infection.[8] Hopefully with increased use of pathogen diagnostic platforms future studies will be able to at least distinguish between viral and bacterial CAP and provide pathogen-specific data on the most common infecting organisms.

Of note, 45% of the patients in the US study had chronic obstructive pulmonary disease (COPD). While patients thought to be suffering from a COPD exacerbation were to be excluded from the study, in the setting of pneumonia, discriminating between patients with and without an acute exacerbation of COPD is subjective

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and likely difficult. Since corticosteroids have proven benefit for patients hospitalized with acute exacerbation of COPD, withholding corticosteroids might have had deleterious effects unrelated to pneumonia, biasing the results in favor of corticosteroids. The lack of a signal in favor of corticosteroids in the US study despite this potential confounder reinforces the credibility of the negative results, and thus increases the imperative to better understand the reasons for the discordant results of the US and French studies.

Having previously been underwhelmed by the evidence for corticosteroids in CAP, the authors believe that the recent high-quality studies have shifted the strength of evidence in favor of early (<24 h) initiation of hydrocortisone in adult patients with severe CAP meeting the criteria used in the French study. That is, respiratory failure requiring at least high flow oxygen, ICU admission and the absence of both septic shock and influenza. Further ongoing trials are needed as the therapeutic window, optimal corticosteroid, optimal dose, optimal duration, and potential gender and pathogen specific effects are all yet to be determined.

Conflict of Interests

The authors state that they have no conflict of interests.

References

1. Waterer G, Metersky ML. Corticosteroids for community-acquired pneumonia: overstated benefits and understated risks. Chest. 2019;156:1049–53.
2. Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019;200:e45–67.
3. Meduri GU, Shih MC, Bridges L, Martin TJ, El-Solh A, Seam N, et al. Low-dose methylprednisolone treatment in critically ill patients with severe community-acquired pneumonia. Intensive Care Med. 2022;48:1009–23.
4. Dequin PF, Meziani F, Quenot JP, Kamel T, Ricard JD, Badie J, et al. Hydrocortisone in severe community-acquired pneumonia. N Engl J Med. 2023;388:1931–41.
5. Fine MJ, Smith MA, Carson CA, Mutha SS, Sankey SS, Weissfeld LA, et al. Prognosis and outcomes of patients with community-acquired pneumonia. A meta-analysis. JAMA. 1996;275:134–41.
6. Group RC, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2021;384:693–704.
7. Ni YN, Chen G, Sun J, Liang BM, Liang ZA. The effect of corticosteroids on mortality of patients with influenza pneumonia: a systematic review and meta-analysis. Crit Care. 2019;23:99.
8. Wirz SA, Blum CA, Schuetz P, Albrich WC, Noppen C, Mueller B, et al. Pathogen- and antibiotic-specific effects of prednisone in community-acquired pneumonia. Eur Respir J. 2016;48:1150–9.

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