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CRITICAL CARE

COMMENTARY

# Corticosteroids for sepsis: registry versus Cochrane systematic review!

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See related research by Beale *et al.*, http://ccforum.com/content/14/3/R102

**Abstract**

A recent report from the PROGRESS registry highlighted that low dose corticosteroids are widely used in patients with sepsis around the world. In this report, corticosteroids may be associated with increased morbidity and mortality. However, these findings should be viewed with caution given that this study has several inherent flaws because of its retrospective nature and the lack of controlled use of corticosteroids. In this commentary, these findings are contrasted with those of a recent Cochrane systematic review.

A recent report from the PROGRESS registry warned readers of potential danger associated with the use of corticosteroids in patients with severe sepsis or septic shock [1]. In this retrospective analysis, 3,051 out of 8,968 (34%) patients received treatment with low dose corticosteroids. Corticosteroid-treated patients were older, had more co-morbidities and greater severity of illness than patients who did not receive corticosteroids. Subsequently, there were more deaths among corticosteroid-treated patients even after controlling for various confounders.

## What is the current evidence on the benefit to risk ratio of corticosteroids in patients with septic shock?

A recent Cochrane systematic review of corticosteroid treatment for severe sepsis and septic shock found 17 randomized controlled trials (n = 2,138) and 3 quasi randomized trials (n = 246) [2]. Computing data from the 17 randomized trials yielded a significant survival benefit from corticosteroids with a risk ratio (RR) of 0.84 (95% confidence interval (CI), 0.71 to 1.00; $P = 0.05$). There was a strong heterogeneity across the studies ($I^2 = 53\%$ by random-effects model), which was mainly explained by differences in treatment strategies. Indeed, the meta-regression using dose and treatment duration showed that survival benefit was strongly dependent on the dose of corticosteroids ($P = 0.02$) - the lower the better - and the duration of treatment ($P = 0.01$) - the longer the better. Then, subgroup analysis based on 12 trials (n = 1,228) of prolonged treatment (5 days or more at full dose) with low dose (lower than 300 mg per day of hydrocortisone or equivalent) corticosteroids found that 28-day mortality for treated versus control patients was 236 out of 629 (37.5%) versus 264 out of 599 (44.1%) (RR, 0.84; 95% CI, 0.72 to 0.97; $P = 0.02$) without heterogeneity across the studies ($I^2 = 15\%$). In this systematic review, there was no evidence for increased risk of gastrointestinal bleeding (n = 1,594; RR, 1.12; 95% CI, 0.81 to 1.53; $P = 0.50$), superinfection (n = 1,917; RR, 1.01; 95% CI, 0.82 to 1.25; $P = 0.92$) or neuromuscular weakness (n = 811; RR, 0.63; 95% CI, 0.12 to 3.35; $P = 0.58$), while corticosteroids were associated with hyperglycaemia (n = 1,434; RR, 1.16; 95% CI, 1.07 to 1.25; $P < 0.001$) and hypernatraemia (n = 805; RR, 1.61; 95% CI, 1.26 to 2.06; $P < 0.001$). Of note, normalizing blood glucose levels in corticosteroid-treated septic shock did not affect mortality [3]. Thus, it is unlikely that corticosteroids increased the risk of death in severe sepsis or septic shock as suggested by Beale and colleagues [1]. Nevertheless, given the opposite findings of the two largest trials of low dose corticosteroids [4,5], which might be explained by differences in severity of illness, current recommendations suggest that low dose corticosteroids should be considered only in patients who are poorly responsive to fluids and vasopressors [6].

## Why should we be cautious in drawing conclusions from the PROGRESS registry?

As highlighted by the authors, this was a retrospective analysis of data from a registry that was set up to assess the routine use of activated protein C and not to investigate the benefit to risk ratio of corticosteroids [1]. Then, there is uncertainty on the modalities of

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corticosteroid treatments. There is no information on the time of treatment initiation, the exact dose and the duration of treatment. Of note, the recent Cochrane systematic review showed that the benefit to risk ratio of corticosteroids was favourably influenced by early treatment, lower doses and longer duration [2]. As the use of corticosteroids was not controlled in patients included in the PROGRESS registry, any conclusion about treatment benefit or harm is severely flawed.

## What should we really worry about?

The most valuable information from the study of Beale and colleagues [1] is the apparently high proportion (14%) of vasopressor-free patients who received treatment with corticosteroids. There is some evidence to support the use of corticosteroids in target populations regardless of the presence of shock, including patients with bacterial meningitis, typhoid fever, pneumocystis pneumonia, or severe community acquired pneumonia [7]. Unfortunately, the study by Beale and colleagues includes no information on the type of infections in the vasopressor-free patients who were treated with corticosteroids. We should worry about the unnecessary use of corticosteroids in patients with sepsis and without shock only in those with infections other than those cited above.

## Where are we now?

There are ongoing trials to confirm the benefit of corticosteroids in septic shock (APROCCHS, NCT00625209) or in severe sepsis without shock (HYPRESS, NCT00670254). While waiting for the results of these trials, the current evidence supports the use of low dose corticosteroids (200 mg of hydrocortisone or equivalent per day for at least 5 days) in patients with septic shock who require 0.25 μg/kg/minute or more of norepinephrine (or equivalent) and in adults with bacterial meningitis or severe community acquired pneumonia.

**Abbreviations**

CI = confidence interval; RR = risk ratio.

**Competing interests**

The author declares that they have no competing interests.

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**References**

1. Beale R, Janes JM, Brunkhorst FM, Dobb G, Levy MM, Martin GS, Ramsay G, Silva E, Sprung CL, Vallet B, Vincent JL, Costigan TM, Leishman AG, Williams MD, Reinhart K: **Global utilization of low-dose corticosteroids in severe sepsis and septic shock: a report from the PROGRESS registry.** *Crit Care* 2010, **14:**R102.
2. Annane D, Bellissant E, Bollaert PE, Briegel J, Confalonieri M, De Gaudio R, Keh D, Kupfer Y, Oppert M, Meduri GU: **Corticosteroids in the treatment of severe sepsis and septic shock in adults: a systematic review.** *JAMA* 2009, **301:**2362-2375.
3. COIITSS Study Investigators, Annane D, Cariou A, Maxime V, Azoulay E, D'honneur G, Timsit JF, Cohen Y, Wolf M, Fartoukh M, Adrie C, Santré C, Bollaert PE, Mathonet A, Amathieu R, Tabah A, Clec'h C, Mayaux J, Lejeune J, Chevret S: **Corticosteroid treatment and intensive insulin therapy for septic shock in adults: a randomized controlled trial.** *JAMA* 2010, **303:**341-348.
4. Annane D, Sébille V, Charpentier C, Bollaert PE, François B, Korach JM, Capellier G, Cohen Y, Azoulay E, Troché G, Chaumet-Riffaud P, Bellissant E: **Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock.** *JAMA* 2002, **288:**862-871.
5. Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K, Weiss YG, Benbenishty J, Kalenka A, Forst H, Laterre PF, Reinhart K, Cuthbertson BH, Payen D, Briegel J; CORTICUS Study Group: **Hydrocortisone therapy for patients with septic shock.** *N Engl J Med* 2008, **358:**111-124.
6. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, Reinhart K, Angus DC, Brun-Buisson C, Beale R, Calandra T, Dhainaut JF, Gerlach H, Harvey M, Marini JJ, Marshall J, Ranieri M, Ramsay G, Sevransky J, Thompson BT, Townsend S, Vender JS, Zimmerman JL, Vincent JL: **Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008.** *Intensive Care Med* 2008, **34:**17-60.
7. Marik PE, Pastores SM, Annane D, Meduri GU, Sprung CL, Arlt W, Keh D, Briegel J, Beishuizen A, Dimopoulou I, Tsagarakis S, Singer M, Chrousos GP, Zaloga G, Bokhari F, Vogeser M; American College of Critical Care Medicine: **Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine.** *Crit Care Med* 2008, **36:**1937-1949.

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