Editorial

Steroids for sepsis: yes, no or maybe

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The rationale for the use of corticosteroids in sepsis, is that this class of drugs downregulates the exuberant and dysfunctional pro-inflammatory response, limits the anti-inflammatory response while at the same time preserving innate immunity (1,2). In 1976, William Schumer published the results of a study where over an 8-year period he randomized 172 patients with septic shock to receive either high-dose methylprednisolone, high-dose dexamethasone or placebo (3). The mortality among the steroid treated group was 14% (24/168) as compared to 42.5% (68/160) in the placebo group (P<0.001). The use of corticosteroids as adjunctive treatment for sepsis has remained a very controversial topic since the publication of this seminal study. Between 1976 and 2017, 21 randomized controlled trials have been published examining the role of short-course high-dose corticosteroid (n=4) and a "low-dose" prolonged course of corticosteroid (usually 200–300 mg hydrocortisone/day for 5–7 days) for patients with sepsis, severe sepsis and septic shock. In all 3,928 patients were enrolled in these 21 studies (average n=357±199). The high-dose regimen was associated with an increased risk of death and increased complications (4). The results of the low-dose regimen were mixed with some studies demonstrating a survival advantage with an improvement in some secondary outcomes while other showed no benefit. Seventeen meta-analyses of these studies have been performed and have similarly shown conflicting results with some demonstrating a survival advantage (4-6) while other have not (7-10). Consequently, true equipoise exists with regards to the clinical benefit of corticosteroids in patients with severe sepsis and septic shock. In order to resolve this important clinical dilemma, the Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock (ADRENAL) trial was performed by the Australian-New Zealand Intensive Care Society Clinical Trials Group (ANZICS) (11). This study was meant to be the "mother" of all trials, enrolling 3,800 patients (equal to the number of patients in all the previous trials combined) and providing the definitive answer to this ongoing controversy. ADRENAL randomized patients with septic shock who were undergoing mechanical ventilation to receive a continuous infusion of hydrocortisone (at a dose of 200 mg per day) or placebo for 7 days. The primary outcome was death from any cause at 90 days.

The ADRENAL study was published/presented in January of 2018 (11). At 90 days, 511 patients (27.9%) in the hydrocortisone group and 526 (28.8%) in the placebo group had died [odds ratio (OR) =0.95; 95% confidence interval (CI), 0.82–1.10; P=0.50]. Furthermore, hydrocortisone had no survival benefit in any of the pre-defined subgroups; however, a number of the secondary end-points favored the hydrocortisone group. Instead of providing the definitive answer to this important question, ADRENAL has generated even more debate (11). It would appear that if you live on the bottom side of the Earth (Australia) you consider this a negative study; however, many of those who live on the top of the world consider it a positive study. So how does one explain the differing interpretations of the same study? There was no difference in the primary end-point of the study (90-day mortality), however, the median time to resolution of shock, median time to discharge from the ICU and the median time to cessation of mechanical ventilation

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were significantly shorter in the hydrocortisone group. In addition, the number of blood transfusion were significantly less in the hydrocortisone group (the explanation for this finding is not entirely clear). Furthermore, the rate of complications (including infections, myopathy and wound dehiscence) were similar in both groups. Although hydrocortisone did not improve patient centered outcomes, many would consider the improvement in secondary outcomes beneficial to patients and the health care system. Additionally, this benefit did not occur at the expense of increased side effects.

It is noteworthy that the 90-day mortality of this large cohort of severely ill patients with septic shock was "only" 28.3%; this is significantly lower than that of recent trials enrolling similar patients with septic shock (12,13). The explanation for this finding is not entirely clear, however, it may reflect the therapeutic approach to septic shock in Australia and New Zealand which includes a conservative approach to fluid management (14-16). The only criticism of the ADRENAL study is that the hydrocortisone was given as a continuous infusion without a loading dose (17); considering the half-life of hydrocortisone, this suggests that it would take between 6 to 12 hours to reach steady state serum concentration. However, a priori analysis of the time to initiation of the infusion did not show a difference in 90-day mortality between the first and last quartiles. In summary, this study confirms the findings of other studies that have demonstrated that a "prolonged" course of low dose corticosteroids has a beneficial biological effect (vasopressor requirement, time on ventilator) without an increase in side effects (5,17). However, the beneficial biologic effects of corticosteroids do not translate into an improvement in important patient centered outcomes. This finding supports our belief that patients with sepsis should be treated with corticosteroids, but not as monotherapy (18). The addition of intravenous Vitamin C and thiamine to corticosteroids enhances the biological effects of corticosteroids with no increase in adverse effects (19,20), and likely improves patient centered outcomes (21).

In acute stress including critical illness, exogenous corticosteroids may have neuro-psychiatric benefits that have been largely ignored. There is a compelling body of literature suggesting that a robust stress response with high corticosteroid activity may act directly and indirectly upon the memory pathways in the brain to reduce the risk of post-traumatic stress disorder (PTSD) (22). In critically ill patients with inadequate corticosteroid activity [Critical Illness Related Corticosteroid Insufficiency (CIRCI)] (2,23), exogenous steroids may protect against the development of PTSD (24,25). Furthermore, low-dose corticosteroids may reduce the risk of delirium in the critically ill. The Hydrocortisone for Prevention of Septic Shock (HYPRESS) study randomized patients with severe sepsis to a continuous infusion of hydrocortisone or placebo for 5 days (17). While treatment with hydrocortisone had no effect on the primary outcome (progression to septic shock) or secondary outcomes, the incidence of delirium was significantly less in the corticosteroid treated group. In this study 11.2% (95% CI, 6.4–19.0) of the corticosteroid treated patients developed delirium as compared to 24.5% (95% CI, 17.2–33.7) of control patients (P=0.01). In addition, much like the ADRENAL study the incidence of side effects (except hyperglycemia) was not increased in the patients treated with hydrocortisone.

Many physicians, particularly surgeons are reluctant to prescribe corticosteroids on the basis that they increase the risk of infections and impair would healing. Both these contentions are incorrect. The prolonged (greater than 10 days) use of moderate- to high-dose corticosteroids (>400 mg hydrocortisone per day) is well known to impair wound healing and increase the risk of opportunistic infections. However, it is likely that a short course of low-dose corticosteroid is not associated with these complications. A short course of preoperative corticosteroid has been shown to attenuate the post-operative inflammatory response which leads to decreased morbidity and shorter length of stay (26-28). In a landmark randomized cross-over study, Keh and colleagues evaluated the clinical and immunological response of "low" dose corticosteroids (240 mg/day hydrocortisone for 3 days) in patients with septic shock (1). In this study hydrocortisone simultaneously decreased circulating levels of both pro- and anti-inflammatory cytokines. Importantly, *in vitro* granulocyte function (respiratory burst and phagocytosis) remained intact, indicating that low-dose hydrocortisone did not suppress innate defense mechanisms. Corticosteroids cause a phenotypic switch of macrophages (M1 to M2) with the differentiation of a specific anti-inflammatory phenotype which is actively involved in resolution of inflammation (29). M2 cells show efficient phagocytic activity, high expression of scavenger receptors and have different chemokine expression profiles compared with M1 macrophages (30,31). In both the ADRENAL study and the HYPRESS studies there was no increased risk of infections, wound dehiscence or any other complication (11,17). Paradoxically, by enhancing macrophage function and blunting the anti-inflammatory

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response short-term corticosteroids may actually reduce the risk of infection. Roquilly and colleagues randomized 149 multi-trauma patients to receive a continuous infusion of hydrocortisone (200 mg/day for 5 days) or placebo (the HYPOLYTE Study) (32). The primary end-point of this study was hospital-acquired pneumonia within 28 days. In the intention to treat analysis, 35% of the patients treated with hydrocortisone and 51% of those treated with placebo developed pneumonia (P=0.007).

Schulze *et al.* performed a randomized, double-blind, placebo-controlled trial that investigated the effects of acute, preoperative corticosteroid administration on cutaneous wound healing (33). In this study of 24 patients, a single dose of 30 mg/kg methylprednisolone (equivalent to about 10,000 mg of hydrocortisone) or placebo was administered intravenously 90 minutes prior to colon resection. There was no difference in wound healing between the two groups. Furthermore, collagen proline levels and the amount of collagen accumulation within the wounds was evaluated over a 10-day period, with no difference between the groups. The results of this study suggest that acute, high-dose corticosteroid administration does not significantly affect wound healing, as determined both clinically and by biochemical parameters. Wang and colleagues reviewed the literature on the association between the use of corticosteroids in the perioperative period and wound healing (34). These authors concluded that "*the preponderance of human literature found that high-dose corticosteroid administration for <10 days has no clinically important effect on wound healing.*"

In summary, the use of corticosteroids in patients with severe sepsis and septic shock is not associated with improved patient centered outcomes, however this treatment is safe and without an increased risk of complications. Corticosteroids appear to have synergistic biological effects when combined with intravenous vitamin C and thiamine and may be associated with improved patient centered outcomes (21). We therefore suggest that the era of glucocorticoid monotherapy as adjunctive therapy in critically ill septic patients has come to an end. This combination therapeutic strategy is being prospectively tested in a number of ongoing randomized controlled clinical trials (clinicaltrials.gov NCT03333278, NCT03335124, NCT03258684, NCT 03380507, NCT03389555, NCT03422159).

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

References

1. Keh D, Boehnke T, Weber-Cartens S, et al. Immunologic and hemodynamic effects of "low-dose" hydrocortisone in septic shock: a double-blind, randomized, placebo-controlled, crossover study. Am J Respir Crit Care Med 2003;167:512-20.
2. Marik PE, Pastores SM, Annane D, et al. 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;36:1937-49.
3. Schumer W. Steroids in the treatment of clinical septic shock. Ann Surg 1976;184:333-41.
4. Minneci PC, Deans KJ, Eichacker PQ, et al. The effects of steroids during sepsis depend on dose and severity of illness: an updated meta-analysis. Clin Microbiol Infect 2009;15:308-18.
5. Annane D, Bellissant E, Bollaert PE, et al. Corticosteroids for treating sepsis. Cochrane Database Syst Rev 2015;12:CD002243.
6. Annane D, Bellissant E, Bollaert PE, et al. Corticosteroids in the treatment of severe sepsis and septic shock in adults: a systematic review. JAMA 2009;301:2362-75.
7. Volbeda M, Wetterslev J, Gluud C, et al. Glucocorticosteroids for sepsis: systematic review with meta-analysis and trial sequential analysis. Intensive Care Med 2015;41:1220-34.
8. Kalil AC, Sun J. Low-dose steroids for septic shock and severe sepsis: the use of Bayesian statistics to resolve clinical trial controversies. Intensive Care Med 2011;37:420-9.
9. Moran JL, Graham PL, Rockliff S, et al. Updating the evidence for the role of corticosteroids in severe sepsis and septic shock: a Bayesian meta-analytic perspective. Crit Care 2010;14:R134.
10. Sligl WI, Milner DA Jr, Sundar S, et al. Safety and efficacy of corticosteroids for the treatment of septic shock: A systematic review and meta-analysis. Clin Infect Dis 2009;49:93-101.
11. Venkatesh B, Finfer S, Cohen J, et al. Adjunctive Glucocorticoid Therapy in Patients with Septic Shock. N

© Journal of Thoracic Disease. All rights reserved.

Engl J Med 2018;378:797-808.
12. Khanna A, English SW, Wang XS, et al. Angiotensin II for the treatment of vasodilatory shock. N Engl J Med 2017;377:419-30.
13. Holst LB, Haase N, Wetterslev J, et al. Lower versus higher hemoglobin threshold for transfusion in septic shock. N Engl J Med 2014;371:1381-91.
14. Hilton AK, Bellomo R. Totem and Taboo: fluids in sepsis. Crit Care 2011;15:164.
15. Reade MC, Huang DT, Bell D, et al. Variability in management of early severe sepsis. Emerg Med J 2010;27:110-5.
16. Hicks P, Cooper DJ, Webb S, et al. The Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008. An assessment by the Australian and New Zealand intensive care society. Anaesth Intensive Care 2008;36:149-51.
17. Keh D, Trips E, Marx G, et al. Effect of Hydrocortisone on Development of Shock Among Patients With Severe Sepsis: The HYPRESS Randomized Clinical Trial. JAMA 2016;316:1775-85.
18. Marik PE. Glucocorticosteroids as Adjunctive Therapy for Acute Respiratory Distress Syndrome and Sepsis? Yes, But Not as Monotherapy. Crit Care Med 2017;45:910-1.
19. Barabutis N, Khangoora V, Marik PE, et al. Hydrocortisone and Ascorbic Acid Synergistically Prevent and Repair Lipopolysaccharide-Induced Pulmonary Endothelial Barrier Dysfunction. Chest 2017;152:954-62.
20. Azari O, Kheirandish R, Azizi S, et al. Protective Effects of Hydrocortisone, Vitamin C and E Alone or in Combination against Renal Ischemia-Reperfusion Injury in Rat. Iran J Pathol 2015;10:272-80.
21. Marik PE, Khangoora V, Rivera R, et al. Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock: A Retrospective Before-After Study. Chest 2017;151:1229-38.
22. Steudte-Schmiedgen S, Kirschbaum C, Alexander N, et al. An integrative model linking traumatization, cortisol dysregulation and posttraumatic stress disorder: Insight from recent hair cortisol findings. Neurosci Biobehav Rev 2016;69:124-35.
23. Annane D, Pastores SM, Arlt W, et al. Critical Illness-Related Corticosteroid Insufficiency (CIRCI): A Narrative Review from a Multispecialty Task Force of the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM). Crit Care Med 2017;45:2089-98.
24. Schelling G, Roozendaal B, Krauseneck T, et al. Efficacy of hydrocortisone in preventing posttraumatic stress disorder following critical illness and major surgery. Ann N Y Acad Sci 2006;1071:46-53.
25. Schelling G, Briegel J, Roozendaal B, et al. The effect of stress doses of hydrocortisone during septic shock on posttraumatic stress disorder in survivors. Biol Psychiatry 2001;50:978-85.
26. de la Motte L, Kehlet H, Vogt K, et al. Preoperative methylprednisolone enhances recovery after endovascular aortic repair: a randomized, double-blind, placebo-controlled clinical trial. Ann Surg 2014;260:540-8; discussion 548-9.
27. Nagelschmidt M, Fu ZX, Saad S, et al. Preoperative high dose methylprednisolone improves patients outcome after abdominal surgery. Eur J Surg 1999;165:971-8.
28. Srinivasa S, Kahokehr AA, Yu TC, et al. Preoperative glucocorticoid use in major abdominal surgery: systematic review and meta-analysis of randomized trials. Ann Surg 2011;254:183-91.
29. Ehrchen J, Steinmüller L, Barczyk K, et al. Glucocorticoids induce differentiation of a specifically activated, anti-inflammatory subtype of human monocytes. Blood 2007;109:1265-74.
30. Bystrom J, Evans I, Newson J, et al. Resolution-phase macrophages possess a unique inflammatory phenotype that is controlled by cAMP. Blood 2008;112:4117-27.
31. Sica A, Mantovani A. Macrophage plasticity and polarization: in vivo veritas. J Clin Invest 2012;122:787-95.
32. Roquilly A, Mahe PJ, Seguin P, et al. Hydrocortisone therapy for patients with multiple trauma: the randomized controlled HYPOLYTE study. JAMA 2011;305:1201-9.
33. Schulze S, Andersen J, Overgaard H, et al. Effect of prednisolone on the systemic response and wound healing after colonic surgery. Arch Surg 1997;132:129-35.
34. Wang AS, Armstrong EJ, Armstrong AW. Corticosteroids and wound healing: clinical considerations in the perioperative period. Am J Surg 2013;206:410-7.

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