Editorial

Corticosteroids for septic shock: what to do now?

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In a recent edition of the *New England Journal of Medicine*, two large randomized controlled trials report on the use of corticosteroids (hydrocortisone) for the treatment of septic shock (1,2). The Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock (ADRENAL) trial failed to show a mortality benefit while the Activated Protein C and Corticosteroids for Human Septic Shock (APROCCHSS) trial showed a significant reduction in 90-day mortality. At first glance it would appear difficult to reconcile these contrasting results; however, I believe there is a logical pathophysiological explanation for these apparent discordant findings. *Table 1* outlines the major differences and similarities between the two studies. It should be noted that in both the ADRENAL and APROCCHSS studies the median time to resolution of shock and median time to discharge from the ICU were significantly shorter in the hydrocortisone group. This finding has been reported in other studies (3), and indicates that corticosteroids have a biological effect in patients with septic shock. Furthermore, both studies demonstrated that corticosteroids did not increase the risk of complications including infections, myopathy and wound dehiscence. Although hydrocortisone did not improve patient centered outcomes in the ADRENAL study, many would consider the improvement in secondary outcomes beneficial to patients and the health care system. The explanation for the mortality reduction in the APROCCHSS study and not the ADRENAL study is likely explained by the fact that patients in the APROCCHSS study had more severe septic shock (as indicated by a higher vasopressor dose and the higher mortality in the control arm), were older (increased risk of death) and included significantly fewer patients with surgical sepsis. In patients with surgical sepsis, the adequacy and timeliness of source control is likely to have a greater effect on patient outcome than adjunctive therapies. These data suggest that while corticosteroids have a beneficial effect on the pathophysiology of septic shock, these drugs only reduce mortality in the sickest subgroup of patients with septic shock. Furthermore, corticosteroids have no proven benefit in patients with severe sepsis (4). These findings support our belief that patients with severe sepsis and septic shock should be treated with corticosteroids, but not as mono-therapy (5). The addition of intravenous vitamin C and thiamine to corticosteroids enhances the biological effects of corticosteroids with no increase in adverse effects (6,7), and likely improves patient centered outcomes (8).

It should be noted that in the ADRENAL study hydrocortisone was given as a continuous infusion (200 mg/day) whereas in the APROCCHSS study hydrocortisone was given as intermittent boluses (50 mg q 6 hourly). Different dosing regimens of corticosteroids likely have distinct therapeutic effects mediated by genomic and non-genomic actions. Several studies have compared glycemic control when hydrocortisone is administered as a bolus compared to a continuous infusion (9,10). These studies have demonstrated more severe hyperglycemia with the bolus regimen. It is well known that the effect of corticosteroids on carbohydrate metabolism (glycogenolysis and glucogenesis) parallel those of the

Table 1 Contrasting characteristics of the ADRENAL and APROCCHSS studies

Variable	ADRENAL	APROCCHSS
Time frame	March 2013–April 2017	September 2008–June 2015
Number patients	3,800	1,241
Number of sites	69	34
Inclusion criteria	Septic shock + vasopressors >4 hours	Septic shock + vasopressors >18 ug/min for >6 hours
Dose	200 mg/day continuous infusion 7 days (no bolus no taper)	50 mg IV q 6 for 7 days (no taper)
Fludrocortisone	No	Yes (50 ug PO daily)
Age, years (steroids *vs.* control)	62.3 *vs.* 62.7	66 *vs.* 66
Pneumonia	33.8% *vs.* 36.8%	58% *vs.* 60%
Surgical admissions	31.2% *vs.* 31.8%	10.9% *vs.* 12.1%
Catecholamine dose >15 ug/min	53.5% *vs.* 55.3%	100%
90-day mortality (steroids *vs.* control)	27.9% *vs.* 28.8%	43.0% *vs.* 49.1%
Faster resolution shock	Yes	Yes
Increased ICU free days	Yes	Yes
Complications		
Hyperglycemia	Yes	Yes
Increased infections	No	No
Wound dehiscence	No	No
Other complications	No	No

drugs anti-inflammatory effects (11). Furthermore, in the study by Loisa *et al.* blood pressure and vascular resistance tended to be higher in the bolus group (9). We therefore postulate that bolus administration of hydrocortisone will result in higher peak levels with greater glucocorticoid receptor binding and consequently have a greater therapeutic effect than when the drug is administered as a continuous infusion. This difference may be more marked in patients with sepsis who have intrinsic glucocorticoid resistance (12). In addition, in the ADRENAL study a loading dose of hydrocortisone was not given; considering the half-life of hydrocortisone, this implies that it would take between 6 to 12 hours to reach steady state serum concentration. It should also be recognized that in the APROCCHSS study, patients in the hydrocortisone arm were also treated oral fludrocortisone (50 ug daily). It is unclear why the authors added fludrocortisone as hydrocortisone has significant mineralocorticoid activity and the oral absorption of fludrocortisone in patients with septic shock is uncertain. Furthermore, in a previous randomized controlled trial, these authors demonstrated no benefit from the combination of hydrocortisone and fludrocortisone as compared to hydrocortisone alone (13).

In summary, although hydrocortisone positively impacts the course of septic shock this drug appears to reduce mortality only in the sickest sub-group of patients. However, we propose that when combined with intravenous vitamin C and thiamine, hydrocortisone improves outcome in all septic patients. We therefore believe that the era of corticosteroid monotherapy to treat sepsis has ended (5). Furthermore, we suggest that hydrocortisone be administered by bolus dosing rather than as a continuous infusion.

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Footnote

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

declare.

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