Adjunctive Corticosteroid Treatment in Septic Shock

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Interest in the role of the adrenal cortex in the recovery from an infection dates back nearly 100 yr. More than six decades of research on the role of corticosteroid supplementation as an adjunctive treatment for sepsis and septic shock failed to reveal conclusive results. Recently two large-scale randomized controlled trials have added substantial new data to inform opinion regarding the role of corticosteroids in the treatment of septic shock.[1,2] In this article, we review the background, the current state of the evidence, and ongoing areas of uncertainty in this field and provide suggestions for clinical practice.

Biologic Rationale for Corticosteroids

There is an established biologic rationale for the administration of adjunctive corticosteroids in the management of patients with septic shock. Septic shock arises as a result of inflammation and vasoplegia from a complex, biologic cascade that is dependent on inter- and intracellular signaling. Corticosteroids are steroid hormones synthesized in the adrenal gland from cholesterol precursors. They are divided into glucocorticoids and mineralocorticoids, which are distinguished by different target cells and effects. Mineralocorticoids have greater effects upon salt and water balance and appear to have a narrower focus of action than glucocorticoids. The biologic rationale for their use includes immune modulation, effects upon cardiovascular tone, and the treatment of relative corticosteroid deficiency. The anti-inflammatory effects of corticosteroids are well established. Corticosteroids modulate the transcription of an array of mainly nuclear factor κB–regulated genes that contribute to inflammation. The synthesis of interleukin-1, interleukin-6, and tumor necrosis factor-α is inhibited, as is inducible cyclooxygenase 2 and inducible nitric-oxide synthase.[3] Corticosteroids also enhance the vasoconstrictor response to vasopressor drugs, in particular exogenous catecholamines. Although the precise mechanism by which this occurs is not known, inhibition of cyclooxygenase 2 and inducible nitric-oxide synthase are likely to play a role.[4] Corticosteroids also mediate catecholamine release from neural cells, and this may partly explain the effect of corticosteroids on the vasculature.[5] Suppression of proinflammatory cytokines and improved circulatory dynamics provide biologic plausibility that corticosteroids may reduce mortality through improved tissue perfusion and metabolic function. A more detailed description of the transcriptomic effect of corticosteroids is beyond the scope of this article, and the interested reader is directed to relevant reviews on the subject.[6] The subject is further complicated by pathophysiological alterations in corticosteroid function that occur in the setting of sepsis. These include changes in concentrations of bound and free cortisol, differential expressions of subtypes of glucocorticoid receptors, and alterations in tissue sensitivity to corticosteroid action.[7,8] These alterations are likely to impact upon our ability to adequately measure adrenocortical function in septic shock and hence add to the difficulty of conducting clinical trials.

Background to the Recent Trials

Randomized controlled trials in the 1980s using high-dose corticosteroids for septic shock, although effective in reversing shock, did not report any mortality benefit.[9,10] There was a resurgence in the use of steroids in septic shock in the 1990s particularly in lower doses (200 to 300 mg of hydrocortisone/day). Although often termed "physiologic doses," this is a misnomer; the normal daily output of cortisol is 40 to 80 μmol/day (*i.e.*, 15 to 30 mg/day). Treatment with so-called "low-dose" hydrocortisone has been documented to increase baseline cortisol levels by a factor of 5, reaching above normal physiologic levels.[11]

The drivers for the renewed interest in steroid treatment were two-fold: the pressor-responsive effect of lower doses of corticosteroids[12] and the description of the syndrome of relative adrenal insufficiency,[13] subsequently termed "critical illness–related corticosteroid insufficiency."[14] This syndrome refers to a group of patients in whom the endogenous adrenal response was insufficient for the degree of stress to which they had been exposed and identified by a blunted cortisol response (less than 9 μg/dl or 248 nmol/l) to corticotropin and termed "nonresponders."

Encouraging results in smaller trials of low-dose steroids in septic shock in the late 1990s[15,16] were followed by two randomized controlled trials: the Ger-Inf-05 in 2002 and the Corticosteroid Therapy of Septic Shock (CORTICUS) trial in 2008. The Ger-Inf-05 trial (n = 299) studied the utility

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of hydrocortisone (200 mg) and fludrocortisone (a synthetic mineralocorticoid; 50 μg/day) compared with placebo for 7 days in patients with septic shock. Shock was reversed more rapidly in the intervention group, and although overall mortality was not reduced, the investigators reported improved survival in patients with a reduced response to corticotropin (63% *vs.* 53%; CI, 0.47 to 0.95; $P = 0.02$).[17]

The European multicenter (CORTICUS) study (n = 499), which evaluated the role of 200 mg of hydrocortisone/day *versus* placebo in patients with septic shock, did not demonstrate any beneficial effect on overall mortality (34% *vs.* 31%; $P = 0.51$) or in the subgroups of corticotropin "responders" or "nonresponders" and reported more episodes of superinfection in the patients who received steroids.[18] The CORTICUS trial had planned on a target enrollment of 800 patients to detect a 10% reduction in mortality in patients who were nonresponders. The study was stopped prematurely when lower than expected recruitment resulted in termination of funding and expiry of the study drug supply. As a result, the trial was significantly underpowered to detect a clinically important treatment effect.

The divergent results from these two trials of low-dose steroids in septic shock (Ger-Inf-05 and CORTICUS) generated substantial debate. Both trials lacked the statistical power to demonstrate a clinically significant reduction in mortality. As noted, the Ger-Inf-05 trial only demonstrated a benefit in patients who failed to respond to corticotropin. These comprised 76.6% of the study population, a percentage that was much larger than the 40% the investigators expected. Statistical significance was only obtained in a survival analysis after adjustment for baseline covariates; in contrast, in-hospital mortality was higher in patients who responded to corticotropin who received hydrocortisone. Additionally, both trials included patients who received etomidate, a short-acting intravenous anesthetic agent that selectively inhibits adrenal corticosteroid synthesis. The effect of etomidate as a confounder in these trials was unclear.

These conflicting results resulted in substantial clinical uncertainty. By 2017, despite more than 20 randomized trials and 11 systematic reviews and meta-analyses, the question of whether corticosteroid treatment produced benefit in septic shock remained unanswered, and surveys revealed widespread variation in clinical practice.[19] However, the design and conduct of these trials was an important influence on subsequent investigations. It was apparent that future trials would have to be substantially larger to address the issue of statistical power and should control for the use of etomidate. There remained uncertainties over the role of fludrocortisone and the corticotrophin test.

Recent Evidence

In 2018, two large multicenter randomized trials (Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock [ADRENAL] and Activated Protein C and Corticosteroids for Human Septic Shock [APROCCHSS]) added substantial new data to inform opinion regarding the role of corticosteroids in the treatment of septic shock (table 1). The ADRENAL trial randomized 3,800 patients with septic shock in 69 intensive care units from five countries to either 200 mg of hydrocortisone administered by infusion or matched placebo. There was no statistically significant difference in the primary outcome of 90-day mortality between the two groups (27.9% *vs.* 28.8%; OR, 0.95; CI, 0.82 to 1.1; $P = 0.5$). However, some of the secondary outcomes were improved in the hydrocortisone group; patients assigned to the hydrocortisone group had earlier shock reversal, faster liberation from mechanical ventilation, reduced frequency of blood transfusion, and earlier discharge from intensive care. There were no significant differences between the treatment groups with respect to 28-day mortality, the rate of recurrence of shock, recurrence of mechanical ventilation, duration and rate of use of renal replacement therapy, time to hospital discharge, the rate of development of new-onset bacteremia or fungemia, and 6-month mortality.[1,20]

The APROCCHSS study was a multicenter, randomized trial conducted in 34 intensive care units in France with a two-by-two factorial design, intended to evaluate the effect of hydrocortisone combined with fludrocortisone, drotrecogin alfa, their respective combinations, and their respective placebos on survival from septic shock. In 2011, after the Prospective Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS)–SHOCK trial,[21] drotrecogin alfa was withdrawn from the market, and the trial continued as a parallel group design comparing hydrocortisone/fludrocortisone against placebo. Of the 1,241 patients randomized, mortality was significantly lower in the group that received hydrocortisone/fludrocortisone (43.0% *vs.* 49.1%; $P = 0.03$). Mortality was lower in the intervention group at intensive care unit and hospital discharge, and at day 180, although not at day 28. The times to weaning from mechanical ventilation, to weaning from vasopressor therapy, and to reach a sequential organ failure assessment score less than 6 were significantly shorter in the hydrocortisone/fludrocortisone group.[2] In contrast to the original Ger-Inf-05 trial, there was no differential treatment effect in the group of corticotropin nonresponders.

The ADRENAL trial reported a higher adverse event rate (predominantly metabolic) in the hydrocortisone group compared to placebo: 1.1% *versus* 0.3%; $P = 0.009$. Specifically, in the treatment group there were six reported episodes of hyperglycemia and three of hypernatremia, compared to three and nil in the placebo group. In contrast, the serious adverse event rate in APROCCHSS was higher but was not significantly different between the two groups: 53.1% *versus* 58.0%; $P = 0.08$. There were no differences in the rates of gastrointestinal bleeding, superinfection, or neurologic sequelae between the APROCCHSS cohorts; however, the rate of hyperglycemia was higher in the intervention group.

Three systematic reviews and meta-analyses incorporating the results from these trials have been published to

Table 1. Comparison of the Major Trials of Adjunctive Corticosteroid Treatment in Septic Shock

	Ger-Inf-05	CORTICUS	ADRENAL	APROCCHSS
Sample size	299	499	3,800	1,241
Inclusion criteria	Septic shock	Septic shock	Septic shock + IPPV	Septic shock (0.25 μg kg^{-1} min^{-1} of noradrenaline)
Medical/surgical, %	66/34	33/66	66/34	80/20
Treatment				
Drugs	HC/FC	HC	HC	HC/FC
Dose per day, mg/μg	200/50	200	200	200/50
Duration, days	7	11	7	7
Mode of administration of HC	Bolus	Bolus	Infusion	Bolus
Tapering	N	Y	N	N
ACTH test	Y	Y	Not performed	Y
Etomidate usage	Y –24%	Y –19%	N	Unspecified
Mortality benefit with HC				
Intention to treat				
In-hospital	N	N	N/A	Y
Day 28	N	N	N	N
Day 90	N	N/A	N	Y
6 months	N/A	N/A	N	Y
12 months	N	N	N/A	N/A
Differential mortality effect in nonresponders to ACTH	Y	N	N/A	N
Other outcomes				
Shock reversal	Y	Y	Y	Y
Weaning from mechanical ventilation	N/A	N/A	Y	Y
Length of ICU stay	N/A	N	Y	N
Length of hospital stay	N/A	N	N	N
Adverse effects with HC	N	Y (superinfections)	Y (metabolic)	Y (metabolic)

ACTH, adrenocorticotropic hormone; FC, fludrocortisone; HC, hydrocortisone; ICU, intensive care unit; IPPV, intermittent positive pressure ventilation; N, no; N/A, not applicable; Y, yes.

date, with some discrepancies in their conclusions. The systematic review and meta-analysis from Rochwerg *et al.*[22] reviewed 42 randomized controlled trials and reported a small effect or no effect on short-term mortality (risk ratio, 0.93; 95% CI, 0.84 to 1.03) and possibly a small reduction in long-term mortality (risk ratio, 0.94; 95% CI, 0.89 to 1.00) with hydrocortisone. In contrast, the systematic review, meta-analysis, and trial sequential analysis restricted to low-dose corticosteroids by Rygård *et al.*[23] reviewed 22 randomized controlled trials and reported no effect on short-term (risk ratio, 0.98; 95% CI, 0.89 to 1.08) or long-term mortality (risk ratio, 0.96; 95% CI, 0.90 to 1.02). Differences in some of the conclusions from these analyses may have arisen from their different inclusion criteria; Rochwerg *et al.*[22] included all trials with children or adults with sepsis treated with any type of corticosteroid in any dose; Rygård *et al.*[23] specified adults with septic shock receiving a dose of less than 500 mg of hydrocortisone equivalent. Although both analyses had a similar statistical analysis plan, Rygård *et al.*[23] included a trial sequential analysis. Additionally, the Rygård article performed their primary analyses only on studies adjudicated to have a low risk of bias, whereas Rochwerg *et al.*[22] included all studies in the primary outcome.

A meta-analysis from Zhu *et al.*[24] also found no effect upon short or long-term mortality. Corticosteroid treatment was associated with a reduction in length of intensive care unit stay in all three reviews and with a reduction in the length of mechanical ventilation and shock in two. Zhu *et al.*[24] reported on no effect of corticosteroid treatment on reversal of shock but did not include either ADRENAL or APROCCHSS in this section of their analysis.

Explanations for the Difference in Mortality Effect

There are several questions arising from the methodologic differences between ADRENAL and APROCCHSS that may explain the observed difference in a mortality effect.

Were the Trial Populations Different?

The ADRENAL trial utilized the 2001 task force definitions (Sepsis-2) of septic shock and additionally mandated a minimum duration of 4 h of vasopressor therapy and the need for mechanical ventilation to be eligible for enrollment. The APROCCHSS trial utilized the 2001 task force definitions of septic shock and mandated a minimum duration of 6 h of vasopressor therapy and a minimum vasopressor dose of 0.25 μg · kg^{-1} · min^{-1} of norepinephrine and evidence of organ failure as defined by a sequential organ failure assessment score of 3 or 4 for at least two organs. Both trials had predominantly "medical sepsis" (patients not admitted directly from the operating room), with similar rates of bacteremia. At baseline, patients in APROCCHSS had a higher mean lactate concentration (4.4 *vs.* 3.8 mM), and a higher proportion were receiving renal replacement

therapy (28.1% *vs.* 12.3%; $P < 0.001$), but a lower proportion required mechanical ventilatory support (91.8% *vs.* 99.9%; $P < 0.001$) as compared to ADRENAL.

These factors, as well as the higher placebo mortality in APROCCHSS compared to ADRENAL (49.1% *vs.* 28.8%; $P < 0.001$), have given rise to the suggestion that the APROCCHSS cohort comprised a sicker group of patients. Although there is no obvious biologic rationale to explain a greater treatment effect of corticosteroids in a sicker cohort, previous data have suggested that this may be the case.[25]

However, a predefined subgroup analysis in the ADRENAL trial showed no mortality benefit in groups dichotomized by APACHE II score higher or lower than 25 or catecholamine dose (more or less than 15 μg/min, equivalent to 0.22 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in a 70-kg individual), and thus no effect based on sickness severity could be observed.

Was the lack of treatment effect on the primary outcome in the ADRENAL trial related to the lower vasopressor dosages? There is no biologic basis to suggest that an arbitrary minimum dose of vasopressors is necessary for corticosteroids to be clinically effective, given the inter- and intraindividual variability in vasopressor responsiveness. As noted above, there was no differential treatment effect on the primary outcome in the subgroups receiving more than 15 μg/min of catecholamines. This would suggest that no threshold level of vasopressor dose is required to commence corticosteroid treatment.

Evidence for Mineralocorticoids

Of the recent, large trials in this area, only the two that combined hydrocortisone and fludrocortisone treatment (Ger-Inf-05 and APROCCHSS) have reported a reduction in mortality. Justifications for including fludrocortisone were the possibility of unrecognized primary adrenal insufficiency, and subsequently the observation that in septic shock the mineralocorticoid receptor may be downregulated.[26] However, there are several reasons to doubt that the addition of fludrocortisone to the treatment regime would confer any additional benefit.

In vitro the mineralocorticoid receptor has an equal affinity for both mineralocorticoids and glucocorticoids and as such would be expected to be activated by circulating cortisol, which is normally found in far higher circulating concentrations than aldosterone.[27] The intracellular isoenzyme 11-β-hydroxysteroid dehydrogenase 2 is found in mineralocorticoid target tissues and converts cortisol to inactive cortisone, thus isolating the mineralocorticoid receptor from cortisol activation. However, the doses of hydrocortisone given for septic shock result in cortisol concentrations of approximately 3,500 mmol/l,[11] which would be anticipated to overload the isoenzyme and activate the mineralocorticoid receptor. This is the basis for the advice that separate fludrocortisone treatment is not required for the treatment of primary adrenal crisis; a daily dose of 50 mg or more of hydrocortisone is equivalent to 0.1 mg of fludrocortisone.[28]

Theoretically, an upregulation of 11-β-hydroxysteroid dehydrogenase 2 activity might explain an additional effect of fludrocortisone in patients with septic shock (fig. 1). However, the limited data available do not support this theory.[29,30]

Furthermore, the short plasma half-life (1.4 h) of fludrocortisone suggests that a single daily dose, as was given in both trials of septic shock, may not be optimal,[31] and there is evidence to suggest that its oral absorption is impaired in critically ill patients; in a study of 21 patients with septic shock administered oral fludrocortisone, plasma levels were undetectable in a third of the patients.[32] Finally, a randomized trial comparing hydrocortisone plus fludrocortisone *versus* hydrocortisone alone in septic shock did not demonstrate any benefit from the addition of fludrocortisone, although the trial was underpowered.[33] In summary, although a definitive answer would only be achieved by an adequately powered randomized trial, we believe the available evidence does not currently support the addition of fludrocortisone to hydrocortisone treatment in septic shock.

Mode of Hydrocortisone Administration

Of the two most recent trials, ADRENAL and APROCCHSS differed primarily in method of drug administration, with ADRENAL specifying a continuous infusion of hydrocortisone compared to the bolus dose approach in APROCCHSS. There are limited data to compare the effects of these alternative delivery strategies. Loisa *et al.*,[34] in a study of hydrocortisone delivered by either bolus or infusion in 48 patients with septic shock, reported no difference in the rate of reversal of shock but more frequent episodes of hyperglycemia in patients receiving hydrocortisone by bolus. An observational trial of 59 patients with septic shock reported that hydrocortisone infusion was associated with a lower maximum dose of norepinephrine compared to bolus administration, as well as a higher proportion of shock reversal.[35] Hydrocortisone infusion has been demonstrated to attenuate the inflammatory response and to reverse shock,[11,16] and the systematic review of Rygård *et al.*[23] found no effect from method of administration on outcome. Infusion is the recommended mode in patients with Addisonian crisis,[36] and practice guidelines for septic shock suggest that infusions may minimize metabolic side effects.[34,37] The use of an infusion may account for the lower rate of adverse effects observed in the ADRENAL trial, but this should be balanced by its greater complexity and need for additional venous access. At present, there is no good evidence to recommend one delivery method over the other. Both trials used equivalent doses of 200 mg/day hydrocortisone. Based on these data, an approach of using a dose of 200 mg/day of hydrocortisone given by either bolus or infusion would be consistent with the available evidence.

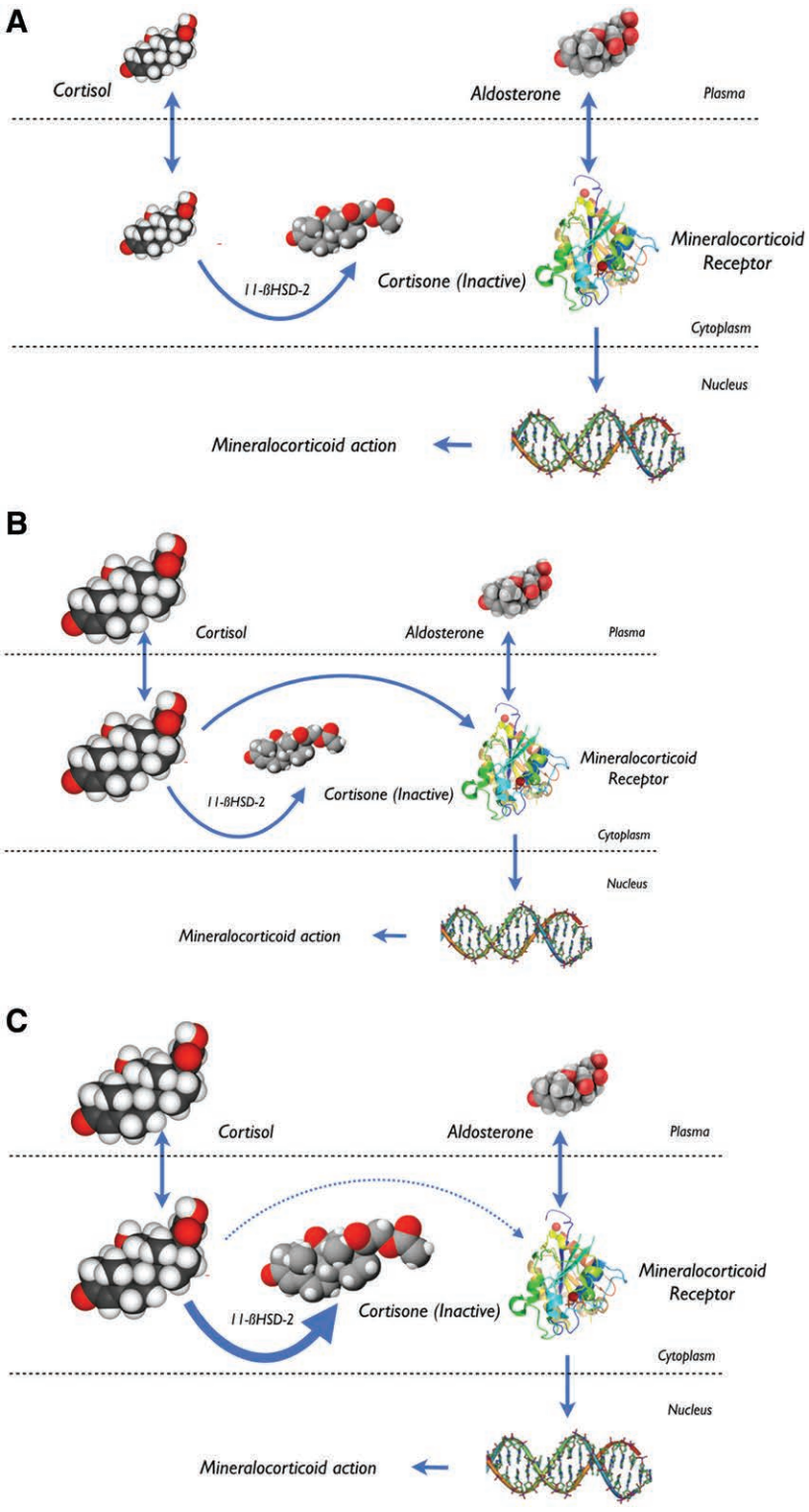

Fig. 1. Effect of 11-β-hydroxysteroid dehydrogenase 2 (11-βHSD2) activity on intracellular metabolism of cortisol in a mineralocorticoid target tissue. (*A*) Normal physiologic conditions. 11-βHSD2 converts cortisol to inactive cortisone, preventing cortisol activation of the mineralocorticoid receptor. (*B*) In the setting of high circulating concentrations of cortisol (pharmacologic doses), the 11-βHSD2 isoenzyme is overloaded, and cortisol can activate the mineralocorticoid receptor. (*C*) (Theoretical) Upregulation of 11-βHSD2 activity inactivates cortisol even in pharmacologic doses, allowing aldosterone to exert separate mineralocorticoid action.

Tapering Strategy

Both recent trials administered 7-day courses of 200 mg of hydrocortisone daily, which were ceased without tapering. A tapering strategy for cessation of corticosteroids has previously been advocated because of the observation of an increase in inflammatory mediators upon abrupt cessation of treatment.[11] However, there was no difference in the rate of recurrence of shock between hydrocortisone and placebo reported in ADRENAL, and tapering had no impact upon outcome as assessed by Rygård *et al.*[1,23] A tapering strategy was not associated with a lower rate of recurrent shock but was associated with hyperglycemia in a recent observational study.[35] Current evidence supports a daily dose of 200 mg of hydrocortisone given for 7 days and ceased without tapering.

Etomidate Use

Etomidate is an anesthetic induction agent that inhibits the 11β-hydroxylase enzyme that converts 11β-deoxycortisol into cortisol and has been shown to induce adrenal insufficiency in critically ill patients.[38] Both CORTICUS and the Ger-Inf-05 trials included patients who had received etomidate (19% and 24%, respectively), and the effect of this potential confounder on the results was unclear.

ADRENAL specified etomidate use as an exclusion criterion; because the drug is not available in Australia where most ADRENAL sites were located, there was very little potential exposure to the agent. As reported in the trial, the numbers of patients receiving etomidate postrandomization was low and not statistically different between the two groups; (1.3% *vs.* 1.2%; $P = 0.88$). The APROCCHSS trial did not specify etomidate as an exclusion criterion and did not report on the proportion of patients who may have been exposed to it.

Is There a Need for Corticotropin Testing?

One of the suggested modes of action of low-dose corticosteroid treatment in septic shock is the treatment of adrenal insufficiency. The concept of relative adrenal insufficiency or, as it has been subsequently termed, critical illness–related corticosteroid insufficiency postulates a state in which the patient's stress response is inadequate for the severity of the illness to which they have been exposed.[14] Patients with critical illness–related corticosteroid insufficiency may have high circulating levels of cortisol but also have an induced state of corticosteroid resistance.

Identification of critical illness–related corticosteroid insufficiency is traditionally suggested to be achieved by performing a short corticotrophin test; this is performed by measuring plasma total cortisol concentrations immediately before and 30 and 60 min after the injection of 250 μg of 1 to 24 adrenocorticotropic hormone. Many diagnostic guidelines have been proposed, but the most recent suggest that an increase in measured cortisol of less than 9 μg/dl (less than 248 nmol/l) indicates critical illness–related corticosteroid insufficiency.

One of the original hypotheses of the Ger-Inf-05 trial was that patients with adrenal insufficiency would be more likely to respond to corticosteroid treatment; the inclusion criteria thus mandated that a short corticotrophin test be performed before randomization. The researchers based their sample size calculations on an incidence of adrenal insufficiency (nonresponders to the corticotrophin test) of 40% and a mortality rate in the placebo arm of nonresponders of 95%, with a 20% mortality reduction with corticosteroids. The incidence of adrenal insufficiency in their cohort was higher than anticipated, 77%, and the observed mortality in this group was 63% in the placebo *versus* 53% in the corticosteroid arm. A beneficial effect on mortality was only observed in the nonresponder group, not in the responder, or full patient cohort.

The 2008 CORTICUS study specified a primary outcome of the rate of death at 28 days in patients who did not have a response to corticotrophin. They reported a nonresponder rate of 46.7%, without any effect on mortality from corticosteroid treatment in either the responder, nonresponder, or total patient groups. Being a responder or nonresponder to corticotrophin did not appear to alter the rate of reversal or the duration of shock. The authors commented that their results suggested that the corticotrophin test was not useful for determining the advisability of corticosteroid treatment in septic shock.

Of the two most recent trials, only APROCCHSS specified a corticotrophin test in the protocol and included an *a priori* subgroup analysis of nonresponders. Because of a shortage of 1 to 24 adrenocorticotropic hormone, the corticotrophin test could only be evaluated in 780 patients out of the total cohort of 1,241. The observed incidence of adrenal insufficiency was 55%, and there was no association between mortality and corticotrophin responder status. The differential treatment effect noted in the Ger-Inf-05 trial by Annane *et al.*[17] was not reproduced in APROCCHSS. At present there is no evidence to support performing a corticotrophin test prior before commencing corticosteroid treatment, and it seems unlikely that further study of the test in this setting would prove to be of benefit.

Adverse Effects

Corticosteroid treatment is associated with numerous adverse effects, including metabolic derangements, gastrointestinal bleeding, neuromuscular weakness, and immunosuppression. It is notable that there was a substantial difference in the rate of adverse effects observed between ADRENAL and APROCCHSS: 0.9% *versus* 56% for the whole trial populations. Neither study protocol explicitly defined specific adverse events; recognition and reporting was at the discretion of the local study investigators. The most frequently observed adverse event in both trials was hyperglycemia, which occurred more frequently in

the intervention group. The two recent meta-analyses that reported on this outcome both indicated that corticosteroid treatment was associated with a higher incidence of hyperglycemia and hypernatremia. Rochwerg *et al.*[22] also reported on a small increase in the rate of neuromuscular weakness associated with corticosteroids. There did not appear to be an increase in the rate of gastrointestinal bleeding or superinfection in any of the pooled analyses. It would appear that overall corticosteroid use may be associated with an increase in minor metabolic derangements, but the likelihood of serious adverse effects from their use is low.

Significance of the Finding of a Reduced Need for Blood Transfusion

An unexpected finding in the ADRENAL trial was the observation of a lower incidence of blood transfusion in the hydrocortisone group (37.0% *vs.* 41.7%; $P = 0.004$). Transfusion was at the discretion of the treating clinician, and no transfusion trigger was specified. This has not been previously reported and may simply represent a type I error. An alternative explanation is that the reduced intensive care unit stay associated with corticosteroid treatment reduces the opportunity for blood transfusions to be prescribed or that the more rapid reversal of shock reduces the amount of fluid resuscitation and consequently hemodilution. Additionally, corticosteroids may have a positive effect on erythropoiesis.[39] At present, this finding should be considered to be hypothesis-generating.

Alignment of Trial Populations with Novel Definitions of Septic Shock

Both ADRENAL and APROCCHSS used the 2001 Task Force definitions of septic shock, which comprised two or more Systemic Inflammatory Response Syndrome (SIRS) criteria, proven or strong suspicion of sepsis, and hypotension persisting despite fluid resuscitation and a need for pressor therapy.[40] A more recent consensus definition (Sepsis-3) was published after both studies had begun recruitment. The new definition suggests that patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mmHg or greater and serum lactate level greater than 2 mM (more than 18 mg/dl) in the absence of hypovolemia.[41]

Not all patients randomized into either trial would necessarily have met Sepsis-3 criteria; in the ADRENAL cohort, it was reported that there were 1,950 (52.5%) subjects who in the 24 h preceding randomization had a mean arterial pressure of less than 65 mmHg and had a plasma lactate concentration of more than 2 mmol: 973 (52.5%) in the hydrocortisone arm and 977 (52.5%) in the placebo arm. Data on the proportion of patients in the APROCCHSS trial fulfilling Sepsis-3 criteria was not reported. A *post hoc* sensitivity analysis exploring this issue would be informative. Currently, benefit from secondary outcomes has been demonstrated in patients fulfilling the 2001 Task Force definitions, suggesting that these criteria would be appropriate ones for clinicians to use in deciding whether to commence adjunctive corticosteroid treatment.

Practice Suggestions

The weight of evidence would suggest that adjunctive corticosteroid therapy may be associated with either no reduction or at best a small reduction in mortality, but there is clear evidence of benefit seen in the patient-centered outcomes of time to withdrawal of ventilation and time in intensive care unit, as well as a faster reversal of shock. This may well be enough impetus for clinicians to prescribe corticosteroids more frequently, especially considering that the reported adverse effects appear to be minor.

Our suggestions are that for clinicians who wish to commence adjunctive corticosteroid treatment for patients with septic shock as defined by the 2001 Task Force definition,

1) Hydrocortisone should be prescribed in a dose of 200 mg/day, for 7 days, by either infusion or bolus.
2) We do not suggest delaying treatment until a threshold dose of vasopressors is reached; corticosteroid treatment can begin within 4 to 6 h of commencement of vasopressor therapy in patients with persisting shock.
3) There is no requirement for dose tapering.
4) There is no requirement to perform a corticotrophin test.
5) Additional fludrocortisone is not necessary.

Summary and Future Questions

There remain a number of questions over the role of corticosteroids in septic shock. In addition to those already discussed, the economic benefits need to be clarified. The cost of a 7-day course of hydrocortisone varies between $20 and $125 depending on the geographic location. A 1-day reduction in intensive care unit length of stay will translate to cost savings of $1,000 to $4,000. If a health economic analysis suggests significant cost savings, irrespective of no change in mortality, this would be an important factor influencing prescribing behavior.

Other avenues of investigation are likely to focus on identifying patients who may be corticosteroid-responsive, either by biochemical or genetic markers. Because of the complexity of corticosteroid actions, candidate gene studies are unlikely to be helpful; however, there is some emerging evidence that genome-wide expression profiling may identify patterns of gene activity associated with response to corticosteroids.[42] Clinical questions remain over the optimum duration of treatment and the role of corticosteroids in relapsing shock, as well as a definitive answer to the role of fludrocortisone. A further large-scale placebo controlled trial with a mortality endpoint seems an unlikely proposition, given the costs and potential loss of equipoise from these recent results. However, comparative investigations into duration or with coadjunctive treatments

such as fludrocortisone are potentially viable avenues of investigation.

In summary, the new evidence provided by ADRENAL and APROCCHSS has given greater certainty to clinicians considering the use of corticosteroid treatment in patients with septic shock. The results from the two recent randomized controlled trials are likely to reinforce the role of adjunctive corticosteroids and change the recommendation in future clinical practice guidelines.

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Competing Interests

The authors declare no competing interests.

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