Corticosteroids for Septic Shock: Another Chapter in the Saga

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Jason Yerke[1], Kyle Strnad[1], and Seth R. Bauer[1]

Abstract

The use of corticosteroids in the management of septic shock has been a highly debated topic for quite some time. Corticosteroids have the ability to combat hyperinflammatory and exaggerated vasodilatory responses, as well as to sensitize adrenergic receptors to decrease the duration of shock. While helpful clinically, this has not translated to consistent mortality benefits. Conflicting results from 2 landmark trials published in 2002 and 2008 have led to varying clinical practices, and a clearly defined role of corticosteroids in septic shock is lacking. A decade later, an influx of new data derived from 2 more large trials continues to echo diverging viewpoints regarding patient mortality. In combination with fluctuating study designs (eg, adjunctive therapies and shock management) and patient populations (eg, illness severity), generalized conclusions are still difficult to draw. Despite these challenges, this review critically analyzes recently published data in the context of historical debate to provide an updated comment on the role of corticosteroids in septic shock. In summary, hydrocortisone therapy is likely to demonstrate maximal benefit when initiated on patients with septic shock and organ failure refractory to vasopressor therapy and should be used judiciously in other settings as it comes without a demonstrated benefit in mortality and increased potential for adverse effects.

Keywords
sepsis, shock, septic, corticosteroids

Introduction

Sepsis and septic shock present a significant global economic, morbidity, and mortality burden, with recent mortality estimates approaching 26%.[1] Annually, an estimated 5.3 million deaths are attributed to sepsis worldwide.[1] Given the dire consequences of this condition, novel therapies to improve sepsis-related outcomes are constantly sought.

During septic shock, an overactive immune response leads to a hyperinflammatory state, causing vasodilation, hypotension, and decreased oxygen delivery to tissues.[2] Consequently, because of their anti-inflammatory properties, corticosteroids are an attractive therapeutic option for the treatment of sepsis-mediated hypotension. Notably, corticosteroids have been shown to inhibit nuclear factor-κB, leading to reduced production of interleukin (IL)-1, IL-6, IL-8, tumor necrosis factor (TNF)-α, and TNF receptors 1 and 2.[3,4] Nitric oxide (NO) is a major mediator of sepsis-induced vasodilation, and corticosteroids have been shown to inhibit inducible NO synthase without affecting constitutive NO production.[3,5] Along with their role in modulating the immune system, corticosteroids increase the sensitivity to certain vasoconstrictors. While the exact mechanism is unknown, it seems to be related to the adrenergic receptors, as administration of corticosteroids has been observed to increase sensitivity to norepinephrine in septic shock patients and to phenylephrine in animal trials.[5,6] In addition, corticosteroids increase angiotensinogen production, angiotensin-converting enzyme activity, and angiotensin type 1 receptor density, leading to increased sensitivity to vasoconstriction mediated through the renin-angiotensin-aldosterone system.[6] Corticosteroids may also increase vasopressin V1 receptors, leading to further vasoconstriction.[7,8]

Early Studies of Corticosteroids

A growing understanding of the pathophysiology of septic shock and the potential role of corticosteroids spurred several clinical trials evaluating clinical outcomes. Most early trials evaluated supraphysiologic corticosteroid doses (≥30mg/kg of intravenous [IV] methylprednisolone) administered in short courses (24 hours or less).[9,10] One meta-analysis of 9 early trials of mainly high-dose corticosteroids in sepsis or septic shock found a trend toward increased mortality in those who received

[1]Cleveland Clinic, OH, USA

Corresponding Author:
Jason Yerke, Medical Intensive Care Clinical Specialist, Department of Pharmacy, Cleveland Clinic, 9500 Euclid Avenue, Hb-105, Cleveland, OH 44195, USA.
Email: yerkej@ccf.org

Table 1. Comparison of Steroid-Treated Patient Baseline Characteristics of Major Trials.

	Annane et al[13] (n = 150)	CORTICUS Sprung et al[14] (n = 251)	ADRENAL Venkatesh et al[15] (n = 1853)	APROCCHSS Annane et al[16] (n = 614)
Catecholamine requirement, μg/kg/min				
Norepinephrine	1.1 ± 1.1[a] (n = 46)	0.5 ± 0.6[b] (n = 224)	N/A[c]	1.02 ± 1.61[a] (n = 534)
Epinephrine	0.8 ± 0.7[a] (n = 41)	0.6 ± 1.2[b] (n = 35)		2.31 ± 6.62[a] (n = 53)
Dopamine	11.2 ± 6.0[a] (n = 136)	10.4 ± 7.5[b] (n = 27)		N/A
Severity of illness				
SAPS II	60 ± 19	49.5 ± 17.8	N/A	56 ± 19
APACHE II	N/A	N/A	24.0 (19.0-29.0)	N/A
SOFA	N/A	10.6 ± 3.4	N/A	12 ± 3
Arterial lactate, mmol/L	4.6 ± 4.4	3.9 ± 3.6 (n = 202)	3.8 ± 3.2[d]	4.4 ± 5.2 (n = 596)
Time from shock onset to first steroid dose, h	4.1 ± 3.4	N/A[e]	20.9 ± 91.9	N/A[f]

Note. All data are presented as mean ± standard deviation or median (interquartile range), as appropriate. CORTICUS = Corticosteroid Therapy of Septic Shock; ADRENAL = Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock; APROCCHSS = Activated Protein C and Corticosteroids for Human Septic Shock; SAPS II = Simplified Acute Physiology Score II; APACHE II = Acute Physiology and Chronic Health Evaluation II; SOFA = Sequential Organ Failure Assessment.

[a]Baseline dose.

[b]Maximum dose.

[c]53.5% of steroid-treated patients had a baseline catecholamine requirement >15 μg/min; mean baseline norepinephrine dose was approximately 29 μg/min.

[d]Highest lactate level.

[e]78.9% of patients received their first dose of steroids within 12 hours of meeting inclusion criteria.

[f]Patients were required to be included within 24 hours of shock onset.

corticosteroids, although there was significant heterogeneity among the trials.[9] More recently, several studies have evaluated low-dose steroids, in an attempt to correct for a theorized "relative adrenal insufficiency." Initial trials showed a decrease in time to shock reversal with hydrocortisone in patients with septic shock.[11,12] These studies, along with a major trial by Annane et al. were evaluated in a 2004 meta-analysis that noted no mortality differences between the corticosteroid and placebo groups.[10,13] However, when analyzing trials published before 1989 with similar trial designs and baseline characteristics (ie, high-dose, short-duration corticosteroid trials), corticosteroids were noted to significantly increase mortality. Trials published between 1997 and 2003 (ie, low-dose, prolonged-duration corticosteroid trials) demonstrated decreased mortality in patients receiving corticosteroids compared with their controls. A significant benefit was also observed in favor of corticosteroid-treated patients in shock reversal in trials post-1997.[10] Given the promising data from early trials of low-dose corticosteroids in septic shock, 4 major trials have been published in the past 17 years, including 2 in 2018. These trials have shaped the use of corticosteroids for septic shock and will be the major focus of this updated review. A comparison of the baseline characteristics and results of these studies can be found in Tables 1 and 2, respectively.

Major Trials of Corticosteroids for Septic Shock

Annane et al[13] analyzed 299 adults with septic shock from 1995 to 1999. In addition to criteria for sepsis, patients must have had a systolic blood pressure <90 mm Hg for at least 1 hour after adequate fluid replacement and dopamine requirements of at least 5 μg/kg/min or any dose of norepinephrine/epinephrine, urine output <0.5 mL/kg for at least 1 hour or a Pao_2:Fio_2 <280, and a lactate >2 mmol/L. All patients were mechanically ventilated and tested for cortisol response after 250 μg IV of adrenocorticotropic hormone (ACTH). Among other criteria, patients were excluded if they had a contraindication or formal indication for steroids. Eligible patients were randomized within 8 hours of shock onset. Patients received hydrocortisone 50 mg IV every 6 hours and enteral fludrocortisone 50 μg daily for 7 days or placebo. Baseline characteristics were similar between groups. The primary end point was the 28-day survival distribution among those patients in the nonresponder group. 28-day mortality among nonresponders was less likely in those who received corticosteroids (adjusted odds ratio [OR] = 0.54, 95% confidence interval (CI) = 0.31-0.97, $P = .04$). No mortality differences were noted among responders or all patients overall. Vasopressors were withdrawn sooner in the treatment arm compared with the placebo arm and were more likely to be withdrawn at day 28. Adverse events were limited and similar between groups. Notably, no difference was noted in the incidence of superinfections or gastrointestinal bleeding. While overall results for this trial were positive, a few points must be noted. First, no difference was noted in 28-day mortality until the results were adjusted for baseline cortisol, cortisol response, McCabe classification, Logistic Organ Dysfunction score, arterial lactate, and Pao_2/Fio_2 ratio. Second, time to appropriate antibiotics in nonresponders was

Table 2. Summary of Major Trials Evaluating the Effect of Corticosteroids on Mortality and Hemodynamic Outcomes in Septic Shock.

	Annane et al[13]			CORTICUS Sprung et al[14]			ADRENAL Venkatesh et al[15]			APROCCHSS Annane et al[16]		
	Steroid (n = 150)	Placebo (n = 149)	*P* (P_a)	Steroid (n = 251)	Placebo (n = 248)	*P* value	Steroid (n = 1853)	Placebo (n = 1860)	*P* value	Steroid (n = 614)	Placebo (n = 627)	*P* value
28-day mortality in nonresponders, No. (%)	60 (53) (n = 114)	73 (63) (n = 115)	.10 (.04)	49 (39.2) (n = 125)	39 (36.1) (n = 108)	.69	N/A	N/A	N/A	N/A	N/A	N/A
Long-term mortality in nonresponders, No. (%)	77 (68)[a] (n = 114)	88 (77)[a] (n = 115)	.13 (.07)	73 (58.9)[a] (n = 124)	60 (57.1)[a] (n = 105)	.89	N/A	N/A	N/A	101 (51.0)[b] (n = 198)	115 (50.4)[b] (n = 228)	.91
28-day mortality in total cohort, No. (%)	82 (55)	91 (61)	.26 (.09)	86 (34.3)	78 (31.5)	.51	410 (22.3) (n = 1841)	448 (24.3) (n = 1840)	.13	207 (33.7)	244 (38.9)	.06
Long-term mortality in total cohort, No. (%)	102 (68)[a]	112 (75)[a]	.17 (.08)	137 (56.6)[a] (n = 242)	127 (54) (n = 235)	.58	511 (27.9) (n = 1832)	526 (28.8) (n = 1826)	.50	264 (43)[b]	308 (49.1)[b]	.03
Time to shock reversal, d	7[c]	9[c]	.01	3.3 (2.9-3.9)[d]	5.8 (5.2-6.9)[d]	<.001	3 (2-5)[e]	4 (2-9)[e]	<.001	N/A[f]	N/A[f]	N/A[f]
Shock reversal, No. (%)	64 (43)[g]	83 (55)[g]	N/A	200 (79.7)[h]	184 (74.2)	.18	N/A	N/A	N/A	N/A[f]	N/A[f]	N/A[f]

Note. CORTICUS = Corticosteroid Therapy of Septic Shock; ADRENAL = Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock; APROCCHSS = Activated Protein C and Corticosteroids for Human Septic Shock; P_a, multivariable analysis adjusted *P* value. CI = confidence interval.

[a]1-year mortality.

[b]90-day mortality.

[c]Hazard ratio = 1.54, 95% CI = 1.10-2.16.

[d]Median (95% CI).

[e]Median (interquartile range).

[f]Vasopressor-free days at day 28: hydrocortisone/fludrocortisone 17 ± 11 vs placebo 15 ± 11, $P < .001$.

[g]Shock reversal by day 28.

[h]Shock reversal at any time point.

prolonged (5.0 ± 9.9 vs 6.3 ± 9.4 hours in the placebo and steroid groups, respectively), which may have increased the overall mortality. However, this likely would have biased the trial toward finding no difference if it affected the trial at all. Overall, this study demonstrated significant benefit of corticosteroids in ACTH nonresponders regarding improved hemodynamics and improved mortality, although significant changes in the approach to treating patients with septic shock since this trial make application of these data potentially challenging.

Changing practices over the next decade stimulated an additional trial involving corticosteroids in septic shock.[16] The APROCCHSS (Activated Protein C and Corticosteroids for Human Septic Shock) trial was originally designed to assess the impact of drotrecogin alfa activated (DAA) and hydrocortisone plus fludrocortisone, alone or in combination. After the withdrawal of DAA from the market, the groups were combined to evaluate hydrocortisone 50 mg IV every 6 hours and enteral fludrocortisone 50 µg for 7 days versus placebo. Neither a benefit from nor interaction with DAA was noted in the study at the time of DAA withdrawal.[17] Adults with indisputable or probable septic shock for less than 24 hours, defined as clinical or microbiologically documented infection, a Sequential Organ Failure Assessment (SOFA) score of at least 3 for 2 or more organs for at least 6 hours, and at least 6 hours of catecholamine therapy (norepinephrine dose of ≥0.25 µg/kg/min or ≥1 mg/h) to maintain a systolic blood pressure of ≥90 mm Hg or mean arterial pressure ≥65, were enrolled. Notable exclusion criteria included life expectancy ≤1 month and current use of 30 mg prednisone equivalents for 1 month or longer. Baseline characteristics were similar between groups. The primary end point assessed was 90-day all-cause mortality. Death occurred in 43% of patients in the treatment group compared with 49.1% in the placebo group (relative risk [RR] = 0.88; CI = 0.78-0.99, P = .03). Steroid-treated patients also experienced lower rates of in-hospital, intensive care unit (ICU), and 180-day mortality (although 28-day mortality was not different) and experienced more vasopressor-free and organ failure–free days at day 28. While it was not the primary analysis, the primary outcome was compared in responders and nonresponders to corticotropin in a subset of patients. Hydrocortisone/fludrocortisone was not superior to placebo in either subpopulation. Aside from hyperglycemia occurring more frequently in the treatment group, adverse effects were not significantly different. Several limitations should be highlighted. First, this study set out to assess a large number of subgroups and secondary outcomes that were ultimately omitted from the results presented in the article for unclear reasons. Second, the findings may lack external validity given the prolonged trial duration (from September 2008 through June 2015), as multiple changes in sepsis management occurred during this time. Overall, this trial demonstrated a positive benefit on 90-day all-cause mortality and shock reversal in favor of the steroid treatment group among patients with septic shock.[16]

In contrast to these 2 studies demonstrating a mortality benefit with corticosteroids, 2 studies did not detect a mortality benefit with this treatment. Following the study by Annane et al. in 2002, Sprung et al[14] published the CORTICUS (Corticosteroid Therapy of Septic Shock) trial in 2008. This was a randomized, double-blind, placebo-controlled trial evaluating adult septic shock patients randomized within 72 hours of shock onset. Exclusion criteria included diagnosis with an underlying disease with a poor prognosis, a life expectancy less than 24 hours, receipt of immunosuppression at baseline, or receipt of long-term corticosteroids within the past 6 months or short-term corticosteroids within the past 4 weeks. Patients were randomized to receive hydrocortisone 50 mg IV every 6 hours for 5 days, then 50 mg IV every 12 hours for 3 days, then 50 mg IV every 24 hours for 3 days, or matched placebo. All patients were tested for response to 250 µg of ACTH. The primary end point was the rate of death at 28 days in ACTH nonresponders. The trial intended to enroll 800 patients; however, only 499 were included due to termination of funding. No significant differences in baseline characteristics were observed when comparing the hydrocortisone and placebo cohorts. Notably, when comparing the entire hydrocortisone group and entire placebo group, Simplified Acute Physiology Score II (SAPS II) and catecholamine requirement were both lower than in other major trials.[13,14,16] No difference was noted in mortality at day 28 between the hydrocortisone and placebo groups in the ACTH nonresponders, responders, or the entire cohort. Similarly, no difference was observed when comparing the treatment groups or any subpopulation regarding mortality at any other time point or the proportion of patients who achieved shock reversal. However, the median time to shock reversal was shorter in the hydrocortisone group compared with placebo among the entire cohort, ACTH responders, and nonresponders. No significant difference in superinfection was noted, although more patients in the hydrocortisone group developed new sepsis or septic shock. Patients receiving corticosteroids were also more likely to develop hyperglycemia and hypernatremia than their placebo counterparts. While this study accounted for some of the limitations of the Annane et al (2002) study, it was not without limitations.[13,14] First, it enrolled only 62.5% of its intended population, leaving it underpowered to detect a clinically meaningful difference in mortality. However, almost no numerical difference was noted in the primary outcome, and it seems unlikely that enrolling the target number of patients the study sought would have led to a different conclusion. In addition, the observed mortality was much lower than predicted, perhaps lessening the treatment effect of steroids. Finally, approximately 25% of patients did not receive appropriate antibiotics, a factor which is known to affect septic shock mortality (although no difference was noted in this trial when comparing patients who did or did not receive appropriate antibiotics).

Table 3. Summary of Recent Meta-analyses Evaluating the Effect of Corticosteroids on Mortality and Hemodynamic Outcomes in Septic Shock.

	Rochwerg et al[18]		Rygård et al[19]	
	RR or MD (95% CI)	I^2	RR or MD (95% CI)	I^2
Short-term mortality	0.93 (0.84 to 1.03)[ab]	38%	0.96 (0.91 to 1.02)[ac]	35%
Long-term mortality	0.94 (0.89 to 1.00)[ad]	0%	0.96 (0.90 to 1.02)[ae]	0%
Time to shock resolution, d	N/A[f]	N/A	−1.52 (−1.71 to 1.32)[g]	51%
ICU length of stay, d	−0.73 (−1.78 to 0.31)[g]	51%	−0.75 (−1.34 to −0.17)[g]	11%

Note. RR = relative risk; MD = mean difference; CI = confidence interval; ICU = intensive care unit.
[a]RR.
[b]Mortality at 28 or 31 days.
[c]Mortality within 90 days; when evaluating only trials at low risk of bias, RR = 0.98, 95% CI = 0.89-1.08, and I^2 = 0%.
[d]Mortality at 60 days to 1 year.
[e]Mortality within 180 days or 1 year.
[f]Shock reversal at day 7, RR = 1.26, 95% CI = 1.12-1.42, and I^2 = 64%.
[g]MD.

The ADRENAL (Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock) trial, published in 2018, was the next major corticosteroid study published after the CORTICUS trial.[14,15] This double-blind, randomized, placebo-controlled trial enrolled adult septic shock patients undergoing mechanical ventilation who had received vasopressors or inotropes for a minimum of 4 hours and continued until the time of randomization. Patients were excluded if they were likely to receive corticosteroids for an indication other than septic shock, were likely to expire within 90 days from a preexisting condition or had treatment limitations in place, or had been eligible for study inclusion for more than 24 hours. Patients were stratified at randomization based on medical versus surgical admission and study center. Patients received a continuous IV infusion of hydrocortisone 200 mg per day for 7 days or until ICU discharge or death, or matched placebo. No ACTH response test was performed. The primary outcome was all-cause 90-day mortality. In total, 3800 patients were enrolled and randomized, and 3658 patients were evaluated for the primary outcome after removing patients who withdrew consent or were lost to follow-up. Baseline characteristics were similar between the hydrocortisone and placebo groups. No significant difference was observed in 90-day all-cause mortality when comparing the hydrocortisone group with the placebo group (OR = 0.95, 95% CI = 0.82-1.10, P = .50). There was no significant heterogeneity in this result noted when evaluating 6 prespecified subgroups, including those with catecholamine requirement above or below 15 µg/min, patients with Acute Physiology and Chronic Health Evaluation II (APACHE II) score of ≥25 or <25, and patients randomized at different time points up to 24 hours from shock onset. There was also no difference in 28-day all-cause mortality. Time to shock resolution was shorter in those receiving hydrocortisone. Time to ICU discharge was shorter in the hydrocortisone group, but no difference was observed in days alive and out of the ICU. A higher proportion of hydrocortisone group patients experienced an adverse event than did placebo patients (1.1% vs 0.3%, P = .0009), although the overall incidence of adverse events in the study was low. Notably, no difference was observed in the rate of new-onset bacteremia or fungemia. Similar to the other major trials, ADRENAL was not free of limitations. First, adverse events were adjudicated by the clinician rather than centrally, leading to possible differences in adverse event reporting. Second, this trial evaluated a hydrocortisone infusion without an initial bolus dose. This may have prolonged the time until hemodynamic response to corticosteroids, potentially minimizing their benefit. In addition, 21 818 patients were screened for 3800 to be randomized, with 8263 patients meeting exclusion criteria. This may have been due to the exclusion criterion of death likely from a preexisting disease within 90 days or treatment limitations in place, which may limit the external validity of the study. Overall, this trial demonstrated improved hemodynamics with the addition of corticosteroids without resultant mortality benefit.

Recent Meta-analyses

Following the completion of the 2 most recent trials, 2 updated meta-analyses have been published.[18,19] A meta-analysis by Rochwerg et al[18] evaluated the effects of corticosteroids in sepsis. Notably, this meta-analysis was not limited to patients with septic shock, and trials of all doses, durations, individual corticosteroids, and additional disease states, totaling 42 randomized controlled trials, were included. The authors concluded that corticosteroids may have a small reduction or no reduction in short-term (28- to 31-day) mortality, but the CI around the estimate included no effect. A potential small benefit was also observed regarding long-term (60-day to 1-year) mortality (Table 3). Corticosteroids increased rates of shock reversal at day 7 and reduced SOFA score at day 7. While corticosteroids did result in slightly shorter ICU and hospital length of stay, these differences

were not statistically significant. Hyperglycemia, hypernatremia, and neuromuscular weakness were more common in corticosteroid patients, although gastrointestinal bleeding, superinfection, and poor neuropsychiatric outcome were not increased. Subgroups, including high- versus low-dose corticosteroids, sepsis versus septic shock, and year of publication were analyzed with meta-regression, with no significant heterogeneity noted in any subgroup analysis. While this meta-analysis provides additional data regarding steroids in sepsis, it has significant limitations. The included trials contain a variety of characteristics (eg, high-dose/short-duration steroids, steroids for longer durations with a primary goal of treating acute respiratory distress syndrome, patients without septic shock) that likely cause significant clinical heterogeneity in included studies and patients. This may have biased the overall result toward the null hypothesis in regard to mortality, similar to what was observed in the meta-analysis by Minneci et al[10] prior to stratifying studies by the publication date/steroid dose. However, no difference was noted when evaluating subgroups, although this was not the primary aim of the meta-analysis.

Rygård et al[19] completed a systematic review and meta-analysis to explore the effects of corticosteroids specifically in patients with septic shock. The study included 22 trials that administered 500 mg of hydrocortisone equivalents or less per day. No difference in short-term mortality was observed when evaluating trials at low risk of bias[15,20] or when evaluating all included trials (Table 3). Of note, the subgroups defined by type of corticosteroid and method of cessation of treatment (ie, abrupt vs tapered) showed potential differential treatment effects. Similar to the primary end point, there was no difference found between the corticosteroid and placebo groups in terms of long-term mortality. The proportion of patients experiencing at least one adverse event was not higher in the corticosteroid group when evaluating all included trials (RR = 0.98, 95% CI = 0.90-1.08, $P = .73$, $I^2 = 54\%$). Tertiary outcomes found that the corticosteroid group, as compared with placebo, had a shorter time to resolution of shock, shorter duration of mechanical ventilation, and shorter duration of ICU stay. Patients receiving corticosteroids were more likely to develop hyperglycemia and hypernatremia, but not secondary infection, gastrointestinal bleeding, or delirium/encephalopathy.[19] Notable strengths of this meta-analysis include its inclusion of only patients with septic shock and its rigorous statistical design. However, pooling of data from studies with differing patient populations (and resultant heterogeneous mortality results) may weaken the external validity of the pooled mortality result.

Discussion and Recommendations

While several major trials and meta-analyses have evaluated the use of corticosteroids in septic shock, many questions remain given the heterogeneity of results, particularly in regard to mortality. First, disparities in study definitions and inclusion criteria led to significant differences in patient populations. Notably, the Annane et al. trial in 2002 and the APROCCHSS trial included patients with multiple organ dysfunctions or patients who could not maintain target blood pressures despite fluid resuscitation and vasopressors.[13,16] The CORTICUS and ADRENAL trials included patients in shock, without specific requirements relating to fluid resuscitation or vasopressors.[14,15] This led to a more severely ill population in the Annane et al. and APROCCHSS trials, particularly in regard to baseline hemodynamic instability as evidenced by vasopressor requirements (Table 1).[13-16] This is echoed by the mortality differences experienced by the control groups in the respective trials.[13-16] Given the improvement in sensitivity to catecholamines following corticosteroid administration, hydrocortisone administration in patients with septic shock not responding to fluids and catecholamines may allow patients to regain adequate perfusion and may account for the difference noted in mortality outcomes. This difference in baseline characteristics of patients in the included studies may have also led to the minimal to no difference observed in mortality outcomes in recent meta-analyses.[18,19] Second, given that the 2 major trials evaluating hydrocortisone in combination with fludrocortisone observed mortality benefit while those evaluating hydrocortisone alone did not, it is reasonable to question whether additional mineralocorticoid activity may be needed to improve mortality.[13-16] While aldosterone increased α_1-adrenergic receptor expression and improved 5-day survival in endotoxemic mice, the only major human clinical trial comparing hydrocortisone plus fludrocortisone with hydrocortisone alone for septic shock observed no difference in any mortality outcome or vasopressor-free days at day 7, and recent meta-analyses found no difference in outcome when comparing different corticosteroid regimens.[18,19,21,22] Finally, another major difference between the trials potentially contributing to the noted heterogeneity is the use of ACTH response testing, given the improvement in mortality in hydrocortisone-treated ACTH nonresponders in the study published in 2002 by Annane et al.[13] However, the CORTICUS study found no benefit of corticosteroids on mortality in responders, nonresponders, or the entire treated cohort.[14] Another found no difference in a subset of patients tested for ACTH response, but found a trend toward lower mortality in steroid-treated patients with response to ACTH (the opposite signal as the study published in 2002 by Annane et al.).[13,16] In addition, the current Surviving Sepsis Campaign guidelines recommend against use of ACTH response testing given these data and possible false measurements when using cortisol immunoassays, leading to inaccurate assignment to response or nonresponse groups.[23]

Given the data presented, multiple factors must be considered before initiating corticosteroids in a patient with septic shock. First, one must consider the goal of corticosteroid therapy. Consistent benefit has been noted across multiple studies in regard to shortening shock duration. We contend

that hemodynamic benefit can be expected across a wide spectrum of septic shock patients regardless of ACTH response status, severity of illness, and use or omission of fludrocortisone. However, the patient population that may derive survival benefit from corticosteroids is much more nuanced. As previously noted, the 2 trials that demonstrated a survival benefit enrolled patients with more significant hemodynamic instability than those that found no mortality benefit. Based on these findings, we suggest that mortality benefit is most likely to be realized in patients who cannot maintain hemodynamic stability with fluid resuscitation and vasopressors alone or in those patients who require moderate doses of norepinephrine and have a SOFA score of 3 or 4 for at least 2 individual organs. Although they were published prior to the 2 most recent studies of corticosteroids, current guidelines are consistent with this recommendation. The most recent Surviving Sepsis Campaign guidelines recommend the use of corticosteroids only in patients who cannot maintain hemodynamic stability through fluid resuscitation and vasopressor therapy.[23] Guidelines from the Society of Critical Care Medicine and European Society of Intensive Care Medicine further specify that corticosteroids should only be used in patients with septic shock that is not responsive to fluids and moderate- to high-dose vasopressor therapy.[24] Second, in patients who are most likely to experience hemodynamic improvement without mortality benefit, the potential risks of adverse events must be considered. The most consistently observed adverse effects in septic shock patients treated with corticosteroids are hyperglycemia and hypernatremia.[14-16,18,19] Because of this, hydrocortisone therapy should be undertaken cautiously in patients with diabetes (particularly those presenting with concomitant diabetic ketoacidosis or hyperosmolar hyperglycemic state) and in those with hypernatremia at baseline. Hyperglycemia associated with corticosteroid therapy may be partially mitigated with the use of a continuous hydrocortisone infusion rather than intermittent boluses.[25] However, comparisons of a bolus dosing strategy with a continuous infusion strategy are not robust in regard to clinical outcomes, and neither major trial that observed mortality benefit utilized a continuous infusion strategy.[13,16,25,26] If a continuous infusion administration strategy is used, it should be initiated with a hydrocortisone bolus of 50 to 100 mg. Perhaps most concerning regarding adverse effects associated with corticosteroids is the small increase in neuromuscular weakness observed in the meta-analysis by Rochwerg et al[18] (RR = 1.21, 95% CI = 1.01-1.52). However, this result was considered to be of low certainty by the authors of the meta-analysis given variability in the timing and method of assessment and variability in the magnitude of effect in the analyzed studies.[18] Notably, there has been no consistent increase in superinfections or death from superinfections in patients treated with low-dose, prolonged-course corticosteroids.[18,19]

In conclusion, we suggest that low-dose hydrocortisone therapy should be administered to patients with septic shock that require moderate- to high-dose vasopressors (more than 30 μg/min of norepinephrine) to maintain hemodynamic stability and have at least one additional (noncardiovascular) organ failure. When the decision to start corticosteroids is made, we suggest hydrocortisone **(**without fludrocortisone**)** at doses of 50 mg IV every 6 hours for 7 days or until vasopressors are no longer needed to maintain hemodynamic stability (whichever is shorter, with no corticosteroid taper). The same dose of corticosteroids may be cautiously considered to shorten shock duration in the remaining population of septic shock patients, although we do not routinely advocate for use in this subpopulation given the lack of consistent mortality benefit associated with shortening shock duration.

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ORCID iDs

Jason Yerke https://orcid.org/0000-0002-4391-9645
Seth R. Bauer https://orcid.org/0000-0002-0420-0320

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