Concise Clinical Review

Systemic Steroids in Severe Sepsis and Septic Shock

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Despite more than 5 decades of study and debate, the role of corticosteroid treatment in patients with severe sepsis and septic shock remains controversial. Data support a beneficial effect on systemic blood pressure in patients with septic shock. However, the ability of corticosteroid therapy to improve mortality in patients with severe sepsis and septic shock remains controversial, with contradictory results from recent large multicenter clinical trials. Although it appears clear that high-dose corticosteroid treatment provides no benefit and possibly harm in septic patients, the experimental design flaws and biases of recent low-dose (physiologic) steroid treatment trials limit their ability to provide adequate answers to the important questions of which septic patients should be treated, how much steroid to give, and the optimum duration of treatment. Unfortunately, the answer to these important questions is not readily evident based on the current evidence or the application of metaanalysis to the available clinical data. This concise evidence-based review highlights the strengths and weaknesses of the current data to inform the practicing clinician as to which patients are likely to derive significant benefit from corticosteroid treatment, while we await more definitive guidance from future multicenter, prospective, randomized, controlled trials designed to better answer these important therapeutic questions.

Keywords: severe sepsis; septic shock; corticosteroid; adrenal function

Severe sepsis and septic shock are common in the critically ill, with a reported incidence ranging from 50 to 300 cases per 100,000 population and mortality rates ranging from 25% up to 70% when complicated by shock and multiple organ failure (1–4). Effective management includes the early administration of appropriate antibiotic therapy and source control, early goal-directed management of hypotension and perfusion abnormalities with fluid resuscitation and vasoactive medication support, and the use of lung-protective ventilatory support strategies, as necessary (5). The prominent role of proinflammatory molecules and pathways suggests a possible therapeutic role for corticosteroid therapy in the management of severe sepsis and septic shock (3). However, despite decades of experimental animal and human trials, the role of corticosteroid therapy, and even the evaluation of the hypothalamic-pituitary-adrenal (HPA) axis in sepsis, remains uncertain and controversial (5–12). Recent consensus statements and metaanalyses have toned down the prior recommendation from Minneci and colleagues that low-dose steroid treatment should be considered for almost all patients with vasopressor-dependent septic shock (5, 13–17). Minneci and colleagues have pointed out potential interactions between severity of illness and response to steroids (13). One thing is quite evident—that there are passionate individuals on both sides of this controversy, and current clinical evidence, including a number of metaanalyses, is not sufficient to provide clear guidance on the important questions of whether corticosteroid therapy is beneficial in patients with severe sepsis and septic shock, what dose to use, and for how long patients require treatment. Other important questions that will need to be addressed, if indeed corticosteroids are found to have a beneficial role in the management of severe sepsis and septic shock, are whether to use intermittent or continuous infusion therapy, whether it is necessary to titrate down the dose versus abrupt discontinuation, and whether a fixed duration of treatment is required or the length of treatment should depend on clinical response. This concise evidence-based review of current available data proposes answers to these questions and informs the practicing clinician on the role for steroids in sepsis management. It is hoped that these comments will help shape future "sepsis management bundles" and provide additional guidance for those who follow the Surviving Sepsis Guidelines (5).

HPA AXIS AND SEPTIC SHOCK

The complex pathophysiologic changes in severe sepsis and septic shock are known to have important impact on endocrine organs with reported alterations in thyroid, pancreas, and adrenal function (18). Treating the hyperglycemia seen in severe sepsis and septic shock with a moderate approach to blood sugar management was associated with improved outcome in comparison to tight glycemic control (19, 20). There have been attempts to correct the hemodynamic derangements seen in septic shock with intravenous levothyroxine (21). By far the most controversial endocrine topic in patients with severe sepsis and septic shock surrounds the optimum method to evaluate adrenal function in these critically ill patients and how to diagnose and subsequently treat those who have corticosteroid insufficiency (22).

The HPA axis is composed of a complex set of positive and negative signals and feedback loops that regulate cortisol synthesis and release (18). Corticotropin-releasing hormone initiates the synthesis of adrenal corticotropin hormone (ACTH) from the anterior pituitary gland, which stimulates the adrenal to produce cortisol (18). Sufficient levels of cortisol production inhibit further production via a negative feedback mechanism. In addition, vasopressin, a neurohormone synthesized in the supraoptic and paraventricular nucleus of the hypothalamus and stored in the posterior pituitary, has been shown to regulate cortisol production via V1a and V1b receptors (18, 23). The majority of cortisol in the circulation is bound to proteins, corticosteroid-binding globulin (70%), and albumin (20%), but the circulating free cortisol is the active form (18, 24). Critical illnesses, such as severe sepsis, are associated with a decrease in albumin and corticosteroid-binding proteins, which

(*Received in original form November 24, 2010; accepted in final form June 2, 2011*)

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Am J Respir Crit Care Med Vol 185, Iss. 2, pp 133–139, Jan 15, 2012

Originally Published in Press as DOI: 10.1164/rccm.201011-1897CI on June 16, 2011
Internet address: www.atsjournals.org

may result in a decreased total cortisol measurement but a relative increase in the free cortisol level (18, 25, 26).

The incidence of adrenal dysfunction during severe sepsis and septic shock has been estimated to be as high as 50% (27). The dysfunction can be either inappropriately low production of glucocorticoids or an impaired response to cortisol in the systemic circulation. Molecular interactions, classified as either genomic or nongenomic pathways, may contribute to impaired cortisol response. The genomic pathways can affect the clinical interaction of cortisol with the glucocorticoid receptor (GR) via either transactivation or transrepression (18, 27). The GR plays an integral role in facilitating the activity of glucocorticoids, and GR-binding affinity has been demonstrated to be altered in severe sepsis and septic shock (18, 27). The nongenomic effects include the interaction of glucocorticoids with vascular membranes, cellular junctions, and the various signaling pathways between cellular mediators (18, 27).

Medications can affect the HPA axis by interacting with corticotropin receptor–binding proteins, disturbing cortisol synthesis, and through direct effects on corticotropin-releasing hormone/ACTH activity (18, 22). Estrogens and estrogen-containing products can increase transcortin, which results in a higher total cortisol but a normal free cortisol. Fluconazole and ketoconazole can affect the synthesis of cortisol, leading to a lower total serum and free cortisol. Etomidate is a carboxylated imidazole, which is used to facilitate endotracheal intubation and has been demonstrated to decrease cortisol synthesis by reversible inhibition of the enzyme 11-β hydroxylase, which is necessary for the final step in cortisol synthesis (28). The effect of etomidate on adrenal function can persist for a period of 24 to 36 hours after the drug has been administered (27). The high incidence of decreased adrenal responsiveness in the Annane and colleagues study may have been partly related to the high use of etomidate in this critically ill septic patient population to facilitate endotracheal intubation (29). A recent study by Jabre and colleagues compared etomidate (0.3 mg/kg) to ketamine (2 mg/kg) for rapid sequence intubation in acutely ill patients and demonstrated a significantly higher percentage of adrenal insufficiency with etomidate versus ketamine, (odds ratio, 6.7; 95% confidence interval [CI], 3.5–12.7) (28). For this trial, the investigators defined adrenal insufficiency as a random cortisol level of less than 10 μg/dl or less than a 9 μg/dl increase in cortisol after an ACTH stimulation test. Prior therapy with oral or inhaled glucocorticoids could predispose a patient to manifest adrenal suppression during critical illness, thereby increasing the probability that adrenal dysfunction could occur during septic shock. For a more in-depth discussion of adrenal function in critical illness the reader is referred to a number of excellent reviews (6, 18, 22).

DIAGNOSTIC ASSESSMENT OF ADRENAL FUNCTION IN PATIENTS WITH SEPTIC SHOCK

Currently, there is a lack of consensus regarding the optimum assessment of adrenal function during septic shock. Evaluation of adrenal function in this setting is complicated by the changes in the amount of circulating free cortisol related to the alterations in the corticosteroid-binding proteins, alteration in the GR-binding protein activity, and albumin concentration (a negative acute phase reactant). The traditional assessment method used in the intensive care unit setting has been the ACTH stimulation test with administration of either 1 μg or 250 μg cosyntropin; however, the sensitivity and specificity of this diagnostic test remain questionable (22, 30). Some investigators have targeted a threshold value of total cortisol with physiologic stimulation (i.e., shock state) or after ACTH stimulation (low or high dose) to identify patients with decreased adrenal function (30). Salgado and colleagues evaluated multiple approaches to diagnose decreased adrenal function in critically ill patients with septic shock and concluded that using the standard 250 μg dose ACTH stimulation test and finding less than or equal to 9 μg/dl increase from baseline in total cortisol 60 minutes after administration was the best predictor of decreased adrenal function (30). In their study of 102 patients with septic shock, 22.5% were found to have adrenal dysfunction based on this diagnostic criterion. Another comparative trial of low-dose versus standard-dose ACTH stimulation of adrenal function found that nonresponders to the low-dose (1 μg ACTH) test had a lower survival rate, and some of these patients would not be evident when tested with standard-dose (250 μg) ACTH (31). It should also be apparent that ACTH stimulation only tests the adrenal response and does not evaluate the HPA axis (18). Although debate continues as to what really defines adrenal dysfunction or insufficiency in patients with septic shock, the current recommendation from the Consensus Task Force of the American College of Critical Care Medicine is that adrenal insufficiency in critically ill patients is best identified by a delta serum cortisol increase of less than 9 μg/dl after a 250 μg ACTH stimulation test or a random total cortisol level less than 10 μg/dl (6, 22). The task force also recommends that this clinical condition may be better termed "critical illness–related corticosteroid insufficiency" (6, 22).

There are also disease interactions that play a role in the manifestation of adrenal dysfunction. For example, HIV, liver failure (hepato-adrenal dysfunction secondary to decreased HDL synthesis needed for cortisol), and cancer can all contribute to the presentation of adrenal dysfunction. Some advocate the use of free cortisol versus total cortisol for assessment of adrenal function (6, 24, 32, 33). Unfortunately, the free cortisol assay is not readily available; therefore, the use of this assay is not yet ready to be incorporated into daily clinical practice. In addition, the interpretation of the results from the free cortisol assay is still conflicting (6, 24, 26).

STEROID THERAPY FOR PATIENTS WITH SEPTIC SHOCK

Over the past 50 years, the pendulum of support has swung back and forth regarding the use of corticosteroid therapy for patients with severe sepsis and septic shock (12, 34, 35). Initial use of steroids was primarily supported by experimental animal data, which demonstrated improvement in survival, even without antibiotic therapy (12). During the mid-1950s through the 1980s it was accepted practice to administer high-dose steroids, using either methylprednisolone (30 mg/kg) or dexamethasone (3–6 mg/kg), in divided doses for 1 to 2 days to treat patients with severe sepsis and septic shock (12, 36, 37). This therapeutic strategy was supported by the results of Schumer's prospective and retrospective studies demonstrating dramatic and significant survival benefit associated with high-dose steroid treatment of septic shock (37). Although these results seemed very impressive, there was concern expressed related to the retrospective part of the study and the long duration of this single-center report (37). In the mid-1980s several prospective, randomized, placebo-controlled clinical trials failed to demonstrate a survival benefit associated with high-dose steroid treatment of severe sepsis and septic shock (38–40). In fact, in selected subpopulations of patients there was a suggestion of possible harm associated with high-dose steroid treatment for sepsis, essentially halting their use for this indication. (15, 34, 35)

However, during the late 1990s data emerged demonstrating that the use of more physiologic steroid treatment (termed

supraphysiologic dose, stress-dose, or low-dose) for patients with septic shock improved hemodynamic parameters and there was a suggestion of improved survival (41–43). Annane and colleagues demonstrated a relationship between the baseline cortisol level of a patient with septic shock and response to a 250 μg ACTH stimulation test and survival (44). They noted an incidence of occult adrenal insufficiency of 54% in this population of patients with septic shock. They also found an 82% mortality rate associated with a basal plasma cortisol level greater than 34 μg/dl and a change of less than or equal to 9 μg/dl after ACTH (Δ max $\leqslant$ 9 μg/dl) (44). In contrast, there was a 74% survival rate in those patients who had a basal plasma cortisol level less than or equal to 34 μg/dl and a Δmax greater than 9 μg/dl. These observations and the suggestion of potential benefit associated with low-dose hydrocortisone in patients with septic shock in small placebo-controlled clinical trials rejuvenated enthusiasm to evaluate low-dose steroid treatment in patients with severe sepsis and septic shock (29, 41–43).

The low-dose corticosteroid trial that resurrected steroid therapy of severe sepsis and septic shock and produced an immediate impact on clinical practice was performed by Annane and colleagues (29). They prospectively randomized 300 patients with septic shock to treatment with either 50 mg of hydrocortisone IV every 6 hours plus fludrocortisone 50 μg daily for 7 days or placebo (29). Patients were randomized within 8 hours of presentation and all had a 250-μg ACTH stimulation at the time of enrollment to evaluate for adrenal dysfunction, defined as less than or equal to 9 μg/dl increase of total cortisol at 60 minutes compared with basal level. The primary end point was 28-day survival distribution from randomization in the ACTH nonresponders. They also evaluated overall mortality, days on vasopressor therapy, and adverse events based on steroid replacement versus placebo. In this trial, 76.5% of the study population met the criteria for ACTH nonresponder (Δmax $\leqslant$ 9 μg/dl) or adrenal dysfunction. Low-dose steroid treatment was demonstrated to reduce time to shock reversal and mortality (29). The 28-day mortality rate in the hydrocortisone-treated nonresponders was 53% versus 63% in the placebo-treated group. Overall there was a significant improvement in 28-day all-cause mortality rate with low-dose steroid treatment (hazard ratio, 0.71; 95% CI, 0.53–0.97; $P = 0.03$) (29) There were no significant differences in adverse events between the two treatment strategies. This study has been criticized for changing enrollment criteria during the trial and the high rate of adrenal dysfunction which may have been related, at least in part, to the use of etomidate to facilitate endotracheal intubation in a majority of the enrolled patients, but may also reflect the higher severity of illness in the enrolled population. The reported improvement in survival coupled with the findings from smaller studies led the 2004 Surviving Sepsis Campaign to support the use of low-dose hydrocortisone for patients with vasopressor-dependent septic shock after adequate fluid resuscitation (45). It now appeared that the pendulum of steroid use had swung in favor of widespread acceptance, particularly because there was no reported significant increase in serious adverse events associated with steroid treatment. Additional support for the use of low-dose hydrocortisone treatment was provided by Oppert and colleagues, who demonstrated an improvement in shock reversal and decreased proinflammatory cytokines in steroid-treated patients with early hyperdynamic septic shock (46). This study compared a bolus of 50 mg of hydrocortisone followed by a continuous infusion of 0.18 mg/kg/h versus placebo. There was no increase in secondary infections between the two treatment strategies, but there was a trend for higher insulin requirement in the hydrocortisone-treated patients (46).

The PROGRESS registry collected data on 12,570 adult patients with severe sepsis at 276 study centers in 37 countries from 2002 to 2005 to evaluate for the use of vasopressor and low-dose corticosteroids (47). Almost 80% of the patients received vasopressor therapy, and 35% were administered low-dose corticosteroids. They found low-dose corticosteroid use to vary by region, with the highest regional use in Europe (more than 50%) and highest individual country use in Brazil (63%). The lowest regional use was Asia (21.6%) and lowest individual country use was seen in Malaysia (9%). They also noted that low-dose steroids were used in 14% of patients with severe sepsis who did not require vasopressor support and would not meet the recommendations of the Surviving Sepsis Guidelines of 2004 or 2008 (5, 45). These data clearly demonstrate that many clinicians throughout the world incorporate low-dose steroid therapy for severe sepsis and septic shock likely related to their belief in the potential safety and efficacy of this therapeutic strategy.

Contributing to the support for low-dose hydrocortisone were several metaanalyses that confirmed a survival and hemodynamic benefit in contrast to the lack of significant benefit and possible harm associated with high-dose steroid strategies (7, 13, 14, 17). The momentum in support of low-dose corticosteroid treatment for severe sepsis and septic shock was steadily gaining until the results of the CORTICUS study were published (48). The CORTICUS trial was a multicenter, prospective, randomized, double-blind, placebo-controlled study of 50 mg of hydrocortisone every 6 hours for 5 days versus placebo in 499 adult patients with septic shock (48). The patients had to have hypotension for at least 1 hour and there was up to a 72-hour enrollment window. The primary end point was 28-day mortality rate in ACTH nonresponders (defined as $<$ 9 μg/dl increase in cortisol after standard-dose ACTH). There was no difference in 28-day mortality between the hydrocortisone and placebo treatment groups (39% vs. 36%, respectively). Shock reversal occurred in 3.3 days in the hydrocortisone treatment arm versus 5.8 days for placebo treatment (48). In addition, the steroid-treated patients had a significantly increased frequency of hyperglycemia, hypernatremia, and superinfections, including new episodes of sepsis (48). Like the Annane and colleagues (29) trial, this study also generated criticism concerning the protocol changes, reduced enrollment, and lower mortality rate compared with prior septic shock studies. The results of prospective, randomized, placebo-controlled, double-blind trials of low-dose corticosteroid treatment of patients with septic shock are listed in Table 1.

Another criticism of the evaluation of corticosteroid treatment in patients with severe sepsis and septic shock is the frequent use of etomidate to facilitate intubation and its potential impact on adrenal response to ACTH stimulation (49). Cuthbertson and colleagues evaluated the 96 patients who were administered etomidate in the 72 hours prior to enrollment in the CORTICUS trial and compared them to the 403 patients who did not receive etomidate in that period (49). They found that the etomidate-treated patients were significantly more likely to be nonresponders to ACTH administration (61 vs. 44.6%, $P = 0.004$) and in a univariate analysis there was an increased mortality associated with etomidate use (odds ratio, 1.70; 95% CI, 1.07–2.68; $P = 0.02$). They also found that the administration of hydrocortisone did not change mortality in the etomidate-treated patients (45 vs. 40%) (49).

The discordant results of the Annane and colleagues and the CORTICUS trials produced uncertainty regarding the merits of low-dose steroid use in patients with severe sepsis and septic shock (29, 48). The fact that there were more adverse events in the steroid-treated group called for a reassessment of the

TABLE 1. PROSPECTIVE, RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND TRIALS OF LOW-DOSE CORTICOSTEROIDS IN PATIENTS WITH SEPTIC SHOCK

Study	Study (*N*)	Study Population	Steroid Treatment	Primary Outcome	28-Day Placebo Mortality (%)	28-Day Treatment Mortality (%)	Conclusion
Bollaert (41)	41	Vasopressor-dependent septic shock on ventilator for >48 h	Hydrocortisone 100 mg q8h for 5 d, then wean over 6 d	Shock reversal	63	32	Hydrocortisone treatment significantly improved hemodynamic abnormalities of septic shock
Briegel (42)	40	Vasopressor-dependent septic shock on ventilator	Hydrocortisone 100 mg load, then 0.18 mg/kg/h continuous infusion until reversal of shock, then wean over 6 d	Shock reversal	30	20	Hydrocortisone treatment significantly decreased time to cessation of vasopressor treatment
Yildiz (43)	40	Patients with sepsis (ACCP-SCCM criteria) (52)	Prednisolone 5 mg at 06:00 and 2.5 mg at 18:00 for 10 d	28-d All-cause mortality	60	40	Trend toward decreased mortality with physiological-dose steroid treatment
Annane (29)	300	Vasopressor-dependent septic shock	Hydrocortisone 50 mg q6h for 7 d and fludrocortisone 50 μg daily for 7 d	28-d Survival distribution from randomization in nonresponders	63	53	Hydrocortisone treatment significantly improved survival and shock reversal in nonresponders to ACTH stimulation test
Oppert (46)	40	Vasopressor-dependent septic shock	Hydrocortisone 50 mg bolus, then 0.18 mg/kg/h until vasopressor discontinued, then wean to 0.06 mg/kg/h for 24 h, then reduced by 0.02 mg/kg/h/d until off	Time to vasopressor discontinuation	48	39	Hydrocortisone treatment significantly improved shock reversal and decreased level of proinflammatory cytokines
Sprung (48)	499	Septic shock	Hydrocortisone 50 mg q6h for 5 d then 50 mg q12h for 3 d, then 50 mg q24h for 3 d	28-d Mortality rate in nonresponders to ACTH stimulation test	36.1 in Nonresponder, 31.5 overall	39.2 in Nonresponder, 34.3 overall	Hydrocortisone treatment did not significantly improve 28-d survival or shock reversal in septic shock nonresponders to ACTH stimulation test

Definition of abbreviations: ACCP = American College of Chest Physicians; ACTH = adrenal corticotropin hormone; SCCM = Society of Critical Care Medicine.

Surviving Sepsis Campaign recommendation. Metaanalyses attempted to provide guidance, but their usefulness is limited by the differences in methodology and patient populations (7, 8, 13, 17). Annane and colleagues evaluated 17 clinical trials in relationship to 28-day mortality and demonstrated a higher mortality rate in control group versus corticosteroid-treated group (38.5 vs. 35.3%, respectively) (50). In addition, the investigators collected data on the incidence of superinfection and hyperglycemia. Elevated blood glucose was the main reported adverse effect, with 51.6% in the corticosteroid arm versus 46% in the placebo arm. This concise review has emphasized the prospective, randomized, controlled clinical trials of steroid treatment of patients with septic shock and did not rely on the multiple metaanalyses that address this issue to avoid problems with systematic errors inherent in many metaanalyses given the differences in patient populations and treatment strategies.

One benefit from the administration of corticosteroids in septic shock is being able to titrate patients off vasoactive therapy earlier (23, 50). Decreased exposure to vasoactive therapy is potentially beneficial for organ function and peripheral vascular circulation recovery. In the VAAST trial, the combination of low-dose vasopressin and corticosteroids was associated with decreased organ dysfunction and mortality in comparison with treatment with norepinephrine and corticosteroids, suggesting a beneficial interaction of steroids and vasopressin treatment (23).

Common corticosteroid treatment regimens include hydrocortisone 100 mg intravenously every 8 hours and 50 mg intravenously every 6 hours. These two treatment strategies have not been evaluated in head-to-head trials. Smaller studies have used continuous infusions of hydrocortisone with beneficial effects noted on hemodynamic function and vasopressor requirement (42, 46). Current Surviving Sepsis Campaign guidelines recommend hydrocortisone in doses not to exceed 300 mg/d for patients with vasopressor-dependent septic shock but do not state a preference of one regimen over another (5). There does not appear to be a difference in efficacy, but there may be differences between the two regimens related to the side effects of immunosuppression and hyperglycemia. The administration of hydrocortisone can be accomplished via intravenous administration or continuous infusion. The rapid intravenous administration provides high spikes in the serum level, does not mimic

natural cortisol secretion, and results in more dramatic changes in blood sugar (27). The continuous infusion administration mimics a more natural physiologic response; however, there appear to be more rebound effects once the corticosteroids have been discontinued (27). In addition, the current recommendations suggest a downward titration of dose after vasopressors are no longer required to prevent any rebound effects of decreased blood pressure and variability in blood glucose values (5, 22).

The role for fludrocortisone therapy in addition to hydrocortisone (which does possess mineralocorticoid activity) was recently evaluated in the COIITSS Trial, which enrolled 509 patients (51). The investigators randomly assigned patients to one of four treatment groups (intensive glucose control with insulin infusion plus hydrocortisone, intensive glucose control with insulin infusion plus hydrocortisone plus fludrocortisone, conventional insulin therapy with hydrocortisone, or conventional insulin infusion plus hydrocortisone and fludrocortisone). The hydrocortisone dose was 50 mg every 6 hours and fludrocortisone 50 μg once daily. They found that intensive insulin therapy was associated with more frequent episodes of severe hypoglycemia (glucose < 40 mg/dl) with the mean number of episodes of 0.15 (95% CI, 0.02–0.28; $P = 0.003$). The rate of survival was 105 out of 245 (42.9%) for fludrocortisone-treated patients versus 121 of 264 (45.8%) for non–fludrocortisone-treated patients. In addition, patients who received fludrocortisone were found to have an increased infection rate, predominantly urinary tract infections. These data suggest that there is no additional survival benefit associated with fludrocortisone treatment and perhaps there may even be an increased risk for increased infection. Based on these findings, we agree with the current recommendations of the Surviving Sepsis Campaign to view fludrocortisone therapy as an optional adjunctive addition to low-dose hydrocortisone in patients with vasopressor-dependent septic shock (5).

These guidelines also suggest that low-dose steroids only be used in fluid-resuscitated vasopressor-dependent patients with septic shock, that there is no need to perform an ACTH stimulation test or other evaluation of adrenal function unless adrenal insufficiency is suspected, and to administer treatment for a 7-day course. At the end of 7 days, the hydrocortisone therapy should be weaned to prevent rebound hypotension. In addition, downward titration of hydrocortisone dose will also result in less variability of blood glucose levels (5, 22).

ADVERSE EVENTS SECONDARY TO STEROID THERAPY IN SEPTIC SHOCK

The major adverse events related to corticosteroid therapy include hyperglycemia, secondary infection from immune suppression, delayed healing, and muscle weakness. High-dose corticosteroid therapy was associated with increased nosocomial infections, but the recent trials with low-dose hydrocortisone treatment have demonstrated conflicting data concerning infection rates. There was a reduced risk of infection in the Annane and colleagues trial, but in the CORTICUS study there was an increase in infection (29, 48). The relative risk for superinfection in the CORTICUS study was 1.27 (95% CI, 0.96–1.68), and the risk of hyperglycemia was 1.18 (95% CI, 1.07–1.31) (48). The COIITSS study reported increased risk of infection when fludrocortisone was added to hydrocortisone treatment (51). Corticosteroid administration is also known to elevate blood sugar, particularly as the steroid dose increases. The presence of hyperglycemia generally triggers clinicians to treat with insulin therapy. Whether the patient is treated with subcutaneous or intravenous insulin, the main risk of insulin therapy is hypoglycemia. The consequences of hypoglycemia can result in alterations in cognitive function and if untreated can be fatal (20). In addition, high-dose steroids result in disruption in skin integrity and delay healing. Another adverse effect of corticosteroid administration is the potential contribution to critical illness polymyoneuropathy (neuromuscular weakness). This disorder can result in prolonged muscular weakness, which may have a dramatic impact on separation from mechanical ventilation and return to independent function. The adverse effect may be potentiated by the concomitant use of neuromuscular blocking drugs (22).

SUMMARY

At this time it remains clear that early high-dose corticosteroid is not helpful and is potentially harmful to patients with severe sepsis and septic shock (13–15, 50). Results from multiple controlled clinical trials clearly demonstrate that low-dose corticosteroid replacement therapy in septic shock is associated with improved blood pressure and shorter duration of vasopressor support in patients with septic shock (13, 14, 29, 40–42, 46, 50). Unfortunately, the available evidence does not permit us to state whether there is a survival benefit associated with the use of lower-dose (physiologic-dose) steroid treatment in patients with vasopressor-dependent septic shock. Recent multicenter trials have failed to definitively answer the question of whether there is an improvement in all-cause 28-day mortality rate associated with the use of low-dose hydrocortisone replacement therapy in patients with vasopressor-dependent septic shock (29, 48). Fludrocortisone does not appear to be a necessary component of this treatment regimen and might be associated with increased infection risk (50). We also remain uncertain as to the optimum low-dose steroid replacement strategy and duration of such treatment, if it is indeed found to be beneficial. In addition, we need further guidance on the best way to diagnose and the clinical impact of the critical illness steroid deficiency syndrome and optimum method to evaluate the HPA axis and/or adrenal function in the setting of critical illness. To provide needed insight into these and other important questions, we are sorely in need of multicenter, prospective, randomized, placebo-controlled, double-blind clinical trials with well-defined inclusion and exclusion criteria to evaluate the potential benefits of corticosteroid treatment and duration in vasopressor-dependent septic shock. These trials should evaluate low-dose physiologic steroid replacement, without fludrocortisone to determine the optimum dose, route of administration (continuous versus intermittent), and duration of treatment (including whether to abruptly stop or taper therapy). Patient management should be controlled by protocol as much as possible to ensure comparability of the treatment groups, and 28-day all-cause survival should be the primary end point. In the absence of additional data to provide guidance, we suggest that the clinicians use their bedside clinical judgement combined with expert opinion to determine the role of corticosteroid treatment in fluid-resuscitated patients with vasopressor-dependent septic shock.

Author disclosures are available with the text of this article at www.atsjournals.org.

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