Steroids for Septic Shock*

Back From the Dead? (Con)

Curtis N. Sessler, MD, FCCP

The role of corticosteroid therapy in the management of septic shock has been debated for half a century. Results from large, well-designed, randomized clinical trials demonstrate no benefit, and perhaps harm, associated with short duration, high-dose methylprednisolone or dexamethasone administered at the onset of septic shock. Based on evidence of “relative adrenal insufficiency” and steroid-responsive adrenergic receptor desensitization in sepsis, administration of modest doses (200 to 300 mg/d) of hydrocortisone for 1 to 3 weeks has been investigated. A multicenter, placebo-controlled clinical trial demonstrated improved survival rates and faster cessation of vasopressors among patients with septic shock who have a poor response to corticotropin injection, consistent with relative adrenal insufficiency. However, concerns regarding a trend for higher mortality among corticotropin responders and the possibility that patients with true adrenal insufficiency may have been enrolled in this placebo-controlled trial, potentially skewing results, should be considered. (CHEST 2003; 123:482S–489S)

Key words: adrenal insufficiency; adrenergic receptor responsiveness; corticosteroid therapy; hydrocortisone; septic shock; supraphysiologic doses; vasopressor support

Abbreviations: CI = confidence interval; HPA = hypothalamic-pituitary-adrenal

The role of systemic administration of corticosteroids on modifying the course and outcome of septic shock has been the subject of considerable debate since the 1950s. Since septic shock remains a common condition associated with substantial morbidity, mortality, and economic cost, there is continued interest in identifying novel agents or new applications of existing drugs that might improve outcome.1 Despite the many proven anti-inflammatory properties of corticosteroids, the wealth of favorable studies utilizing various animal models of septic shock, and many anecdotal positive reports in clinical sepsis, multicenter clinical trials have generally failed to support this form of treatment. Clinical trials2–4 again raise the possibility that corticosteroids might improve outcomes from severe sepsis. These new investigations, however, differ from previous approaches, since relative low doses of corticosteroids are administered over longer time periods. Further, although traditional reasoning emphasized the anti-inflammatory properties of corticosteroids in blunting the “inflammation run amok” of early septic shock, evidence suggests that occult impaired adrenal functional reserve and reduced adrenergic receptor responsiveness might be targets for physiologic doses of corticosteroids.5–11 These new reports, while provocative, deserve careful scrutiny prior to acceptance into clinical practice.

EARLY CLINICAL TRIALS

The convoluted course of enthusiasm and skepticism for using corticosteroids in sepsis is striking and dates to uncontrolled reports in the 1950s of improved outcomes in a variety of severe infections. In 1974, Weitzman and Berger12 systematically reviewed 32 original clinical investigations, published from 1950 to 1971, that addressed the use of corticosteroids in bacterial infections. They carefully examined each article for adherence to standards for proper experimental design and interpretation and found that exceedingly few met acceptable standards. Of the 12 studies that addressed septic shock, 9 advocated the use of corticosteroids and 3 concluded that steroids were not beneficial. Only two of the favorable studies and 1 unfavorable study were prospective, and only a single unfavorable study was randomized and double blinded. The authors concluded that properly designed studies must be performed before the controversy can be resolved.

Two years later, Schumer13 published a report in which very impressive reductions in mortality were demonstrated for patients with septic shock treated with corticosteroids. Mortality rates of 11.6% and 9.3% were seen for patients treated with methylprednisolone (one or two doses of 30 mg/kg IV) and dexamethasone (one or two doses of 3 mg/kg IV), respectively, vs 38.4% for patients receiving placebo. A concomitantly performed “retrospective” study13 showed similar results. Based on this report, it became standard practice in the late 1970s and early 1980s to administer high-dose corticosteroids at the onset of septic shock. Closer examination of the report, however, revealed numerous concerns in study design and interpretation. In this study, a single investigator enrolled a total of 500 patients in either a “prospective” (n = 172) or a concomitant retrospective study (n = 328) on a surgical service at one hospital over a 9-year period. In the prospective study, patients who had either “a septic history,” “a falling BP,” or positive blood culture results were randomized by a card system into the three treatment groups. The primary outcome was death attributable to septic shock, described as “... if the patient succumbed immediately to the shock episode or had a continuing septic course with episodes of shock and then succumbed.”13 The lack of blinding, subjective entry and end point criteria, concomitant prospective and retrospective

*From the Division of Pulmonary and Critical Care Medicine, Virginia Commonwealth University Health System, Medical College of Virginia Hospitals, Richmond, VA.
Reproduction of this article is prohibited without written permission from the American College of Chest Physicians (e-mail: permissions@chestnet.org).
Correspondence to: Curtis N. Sessler, MD, FCCP, Division of Pulmonary and Critical Care Medicine, Medical College of Virginia at Virginia Commonwealth University, Box 980050, Richmond, VA 23298; e-mail: cessler@vcu.edu

Conundrums in Management of Critically Ill Patients

482S
studies, and other design flaws presented multiple opportunities for bias to affect the results and caused concern about their validity.

**Large, Randomized Clinical Trials of High-Dose Corticosteroids in Septic Shock**

The 1980s brought several well-designed, single-center studies as well as two large, multicenter clinical trials.\(^{14-17}\) In an open-label trial, Sprung and colleagues\(^{14}\) randomized 59 patients to receive methylprednisolone, 30 mg/kg IV, dexamethasone, 6 mg/kg IV, or placebo. Objective criteria for septic shock closely approximated current consensus criteria, and outcome measures were well established. They demonstrated more rapid shock reversal as well as survival benefit at 6 days after drug administration with corticosteroids. This survival benefit disappeared, however, when patients were followed up beyond 10 days. In another single-center study, Luce and colleagues\(^{15}\) found no improvement in survival or prevalence of ARDS in a double-blind comparison of methylprednisolone (four 30 mg/kg doses over 24 h) vs placebo in 75 septic patients.

The results of two large, multicenter clinical trials of steroids in sepsis were published in 1987. In the Veterans Administration trial,\(^{16}\) 233 patients were randomized in a double-blind fashion to methylprednisolone, 30 mg/kg followed by 5 mg/kg, or to placebo, administered within 3 h of diagnosis. No difference in 14-day mortality or complications was demonstrated. In the largest clinical trial, Bone and co-investigators\(^{17}\) randomized 381 patients to receive methylprednisolone, 30 mg/kg, or placebo. Patients who received methylprednisolone had a higher mortality rate than the placebo group. As a result of these pivotal multicenter clinical trials, the use of corticosteroids for septic shock fell out of favor. Reviews and critical care textbooks in the 1990s have generally cautioned against the use of supraphysiologic doses of corticosteroids in septic shock.

In 1995, two meta-analyses of clinical trials of steroids in sepsis were reported.\(^{18,19}\) In each, the published reports were distilled down to 9 or 10 randomized controlled trials of corticosteroids in sepsis and septic shock. Cronin and colleagues\(^{18}\) rated each of nine studies in 11 categories for methodologic quality and calculated the relative risk for mortality. The common relative risk for overall mortality in 1,232 patients with sepsis or septic shock was 1.13, with 95% confidence intervals (CIs) of 0.99 and 1.29 in favor of control therapy, significant at \(p = 0.02\). The relative risk for overall mortality in patients with septic shock only was 1.07 (CI, 0.91 to 1.26), \(p = 0.06\). This analysis suggests that there is no treatment advantage, and perhaps harm, associated with corticosteroids therapy for sepsis and septic shock. Lefering and Neugebauer\(^{19}\) expressed the effect of corticosteroid treatment as the difference in mortality rates between treatment and control groups and demonstrated a pooled difference of only \(-0.2%\) with CIs of \(-9.2\%\) and \(-8.8\%,\) concluding there is no treatment advantage or harm associated with corticosteroids.

**Relative Adrenal Insufficiency and Randomized Clinical Trials of Moderate Doses of Corticosteroids**

Despite convincing evidence that corticosteroids administered in supraphysiologic doses early in sepsis are not effective, and might even be harmful, renewed interest in corticosteroid therapy, now in the context of relative adrenal insufficiency, has emerged. A number of studies\(^{5-10}\) demonstrated that patients with septic shock, particularly those with severe or fatal shock, often had high serum cortisol levels, but associated with a blunted cortisol response to stimulation with corticotropin. These findings have been interpreted as evidence of “relative adrenal insufficiency” and are linked to worse outcomes in septic shock.\(^{5-10}\) Uncontrolled, small case series\(^{20-22}\) depicting rapid shock reversal accompanying low-dose hydrocortisone infusion in septic shock appeared in the 1990s.

The results of two single-center and one multicenter, prospective, randomized, double-blind, placebo-controlled clinical trials performed in European hospitals demonstrated more rapid recovery from shock and other favorable outcomes with hydrocortisone treatment.\(^{5-4}\) Bollaert and colleagues\(^{2}\) randomized 41 patients from two ICUs of a French university hospital to hydrocortisone (100 mg IV tid for 5 days, then reduced by half every 3 days) or placebo. To be enrolled, patients must have met American College of Chest Physicians/Society of Critical Care Medicine consensus criteria for septic shock,\(^{23}\) had a post-corticotropin cortisol plasma concentration of > 18 μg/dL (excluding adrenal insufficiency), and have received vasoressor support for > 48 h. This novel approach selected patients with persistent septic shock, in striking contrast to previous studies in which steroids were administrated immediately after shock was diagnosed. Sixty-eight percent of hydrocortisone-treated patients and 21% of placebo-treated patients achieved shock reversal (stable systolic arterial pressure > 90 mm Hg for ≥ 24 h without catecholamine or fluid infusion) \([p = 0.007]\). There was a strong trend toward improved survival, with 28-day mortality of 32% in the hydrocortisone group and 63% in the placebo group \((p = 0.091)\). Complications such as GI bleeding and secondary infections were infrequent and similar between groups. Despite these encouraging findings, there are important concerns. The duration of shock prior to enrollment was prolonged and highly variable with a mean of 6 days. Although the two treatment groups were well matched in most regards, the placebo group had generally higher baseline cortisol levels (hydrocortisone group, 21 μg/dL; placebo group, 30 μg/dL) as well as more corticotropin nonresponders (hydrocortisone group, 4 of 22 nonresponders; placebo group, 8 of 19 nonresponders). Amann and colleagues\(^{10}\) showed that septic shock patients with this pattern of high basal cortisol and poor response to corticotropin had a very poor outcome, with a 28-day mortality rate exceeding 80%. Thus, in this small study, the worse outcome in the placebo group may be explained in part by the underlying hypothalamic-pituitary-adrenal (HPA) axis status. Although a significant change in catecholamine dosage was demonstrated be-
tween the two groups, this is largely the result of an unexplained 40% increase in catecholamine dosage in the placebo group at 24 h.

Briegel and colleagues\(^3\) prospectively randomized 40 patients with septic shock by American College of Chest Physicians/Society of Critical Care Medicine criteria in one German ICU to receive placebo or a hydrocortisone 100-mg infusion followed by 0.18 mg/kg/h IV for at least 6 days, then tapered by protocol over 6 days after shock reversal. Patients were further selected for hyperdynamic sepsis (cardiac index > 4 L/min/m\(^2\)) and were excluded if vasopressors were used for > 72 h. The two groups were similar at baseline. The hydrocortisone group had higher mean arterial pressure and systemic vascular resistance, and lower cardiac index and oxygen delivery during the first 5 days of treatment. The time for stopping vasopressor infusion was shorter, and there was a trend for an improved sequential organ failure assessment score in the hydrocortisone group. Four of 20 hydrocortisone-infused and 6 of 20 placebo-infused patients died in the ICU (p = 0.72). Patients who received this prolonged course of hydrocortisone had significantly higher serum sodium, alanine aminotransferase, and increases in urea nitrogen and blood glucose. It is important to consider that concomitant routine management of patients enrolled in the study included selective nasopharyngeal and gut decontamination, routine antithrombin III administration if the antithrombin III level was < 70%, continuous infusion of unfractionated heparin, and polyvalent Ig if Gram-negative infection was diagnosed. These therapeutic measures are certainly not routinely administered in the management of septic shock by most intensivists, and thus the ability to confidently apply the results to other populations is limited.

Annane and colleagues\(^4\) recently published the results of a multicenter placebo-controlled clinical trial performed in 19 French ICUs, in which the effects of a 7-day course of IV hydrocortisone, 50 mg q6h, plus daily oral fludrocortisone on outcomes of patients with septic shock are described. Three hundred patients who met stringent criteria for septic shock (including hypotension with vasopressor use, organ dysfunction, and mechanical ventilation) were enrolled over 41 months. A priori, patients were categorized as “responders,” who manifested an increase in plasma cortisol level > 9 µg/dL from baseline after a short corticotropin test, or “nonresponders,” who had a change in plasma cortisol level that did not achieve this magnitude of cortisol response. The groups were well matched in regard to clinical characteristics, severity of illness, and infection characteristics. Twenty-eight-day survival distribution in nonresponders, whom the authors considered to have relative adrenal insufficiency, was the primary end point. Among the 229 nonresponders, there were more deaths at 28 days in placebo-treated patients (63%) than in the corticosteroid-treated patients (53%), with a hazard ratio of 0.67 (95% CI, 0.47 to 0.95; p = 0.02). Vasopressor therapy was withdrawn within 28 days in 40% of nonresponder patients in the placebo group and in 57% of patients in the corticosteroid group, with a hazard ratio of 1.91 (95% CI, 1.29 to 2.84; p = 0.001). Among the 299 patients, the hazard ratio for death was 0.71 and for vasopressor withdrawal was 1.54, both p < 0.05, favoring steroid therapy. Adverse events were similar for the two treatment groups, although effects on blood glucose are not reported.

Although this multicenter trial was well designed and conducted, there are important concerns that influence interpretation of the primary results. First, some subjects enrolled in this placebo-controlled clinical trial may, in fact, have had not just “relative” adrenal insufficiency, but true primary or secondary adrenal insufficiency. In contrast to some studies,\(^2\) patients who had post-corticotropin plasma cortisol levels 18 µg/dL (a cutoff value commonly used to exclude adrenal insufficiency\(^24,25\)) were enrolled in this clinical trial.\(^4\) Previous studies\(^6,8,26,27\) that examined HPA axis function in septic shock demonstrated that 6 to 25% of consecutively tested patients had post-corticotropin plasma cortisol levels < 18 µg/dL. Further, the clinical presentation of acute adrenal crisis can easily be mistaken for septic shock.\(^23,26,29\) Unlike relative adrenal insufficiency, for which the role of steroids remains debated, the administration of corticosteroids is strongly recommended for suspected acute adrenal insufficiency with shock.\(^24,29\) Accordingly, it would be of interest to examine the prevalence, and outcome, of placebo-treated patients who had peak plasma cortisol levels < 18 µg/dL in this study.\(^3\) Worse-than-expected outcomes of patients with actual adrenal insufficiency who were entered into the placebo study arm and therefore did not receive corticosteroids could have contributed to the observed treatment benefit attributed to hydrocortisone in septic shock.

Secondly, the adjustments made to the key statistical analyses, while prospectively designed, may have statistically inflated the treatment benefit of corticosteroids. Based on previous work,\(^10\) the authors performed testing of hazard ratios and odds ratios for fatal events after adjusting for a variety of factors that include baseline cortisol, response to short corticotropin test, McCabe score, logistic organ dysfunction system score, arterial lactate levels, and Pa\(_O_2/\text{fraction of inspired oxygen. Yet, other than a higher corticotropin response for steroid-treated patients in the “all patients” category, there were no statistically significant differences between placebo and steroid treatment groups within the nonresponder, responder, and all patients categories for any of the six variables used in the adjustment model. This adjustment appears to favor the sepsis treatment arm. For example, among the responders, the mortality rate was higher in the steroid group (61%, vs 53% for the placebo group), yet the adjusted odds ratio was calculated to be 0.97 (CI, 0.32 to 2.99), slightly favoring the steroid group. However, the unadjusted relative risk for death in the responder group is calculated to be 1.15 (95% CI, 0.77 to 1.74). When relative risk for death, not adjusted for the above-noted variables, is calculated, the values continue to favor hydrocortisone for nonresponders and for all patients (relative risk, 0.83 and 0.90, respectively). However, the upper 95% CI is > 1.0 for both groups (Table 1), supporting only a trend for benefit with corticosteroids.
<table>
<thead>
<tr>
<th>Source/Year</th>
<th>Patients, No.</th>
<th>Mortality: Relative Risk (95% CI)†</th>
<th>Quality Score‡</th>
<th>Drug/Dose</th>
<th>Day 1 Corticosteroid Dosage, mg/kg MP equivalents§</th>
<th>Total Corticosteroid Dosage, mg MP equivalents§</th>
<th>Duration of Treatment, d</th>
<th>Approximate Lag Time From Diagnosis to Treatment, h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bennet and Finland, 1963</td>
<td>194</td>
<td>1.72 (1.23–2.41)</td>
<td>4.0</td>
<td>HC, 300 mg, then 50 mg/d for 6 d</td>
<td>1.0</td>
<td>1.7</td>
<td>6</td>
<td>N/A</td>
</tr>
<tr>
<td>Klastersky et al, 1971</td>
<td>85</td>
<td>0.97 (0.65–1.45)</td>
<td>5.0</td>
<td>B, 1 mg/kg/d for 3 d</td>
<td>4</td>
<td>12</td>
<td>3</td>
<td>N/A</td>
</tr>
<tr>
<td>Schumer, 1976</td>
<td>172</td>
<td>0.30 (0.13–0.72)</td>
<td>6.0</td>
<td>MP, 30 mg/kg, repeated once after 4 h if necessary DEX, 3 mg/kg, repeated once after 4 h if necessary</td>
<td>45</td>
<td>45</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Thompson et al, 1978</td>
<td>60</td>
<td>1.01 (0.77–1.31)</td>
<td>12.0</td>
<td>MP, 30 mg/kg</td>
<td>30</td>
<td>30</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Lucas and Ledgerwood, 1984</td>
<td>48</td>
<td>1.09 (0.36–3.27)</td>
<td>4.0</td>
<td>DEX, 2 mg/kg, 6 mg/kg for 48 h by continuous infusion</td>
<td>12</td>
<td>24</td>
<td>2</td>
<td>N/A</td>
</tr>
<tr>
<td>Sprung et al, 1984</td>
<td>59</td>
<td>1.11 (0.74–1.67)</td>
<td>9.5</td>
<td>MP, 30 mg/kg, repeated once after 4 h if necessary DEX, 6 mg/kg, repeated once after 4 h if necessary</td>
<td>57</td>
<td>57</td>
<td>1</td>
<td>18</td>
</tr>
<tr>
<td>Veterans Administration, 1987</td>
<td>223</td>
<td>0.95 (0.57–1.58)</td>
<td>10.5</td>
<td>MP, 30 mg/kg followed by 5 mg/kg</td>
<td>35</td>
<td>35</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Bone et al, 1987</td>
<td>381</td>
<td>1.35 (0.98–1.84)</td>
<td>11.5</td>
<td>MP, 30 mg/kg</td>
<td>30</td>
<td>30</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Lucas et al, 1985</td>
<td>75</td>
<td>1.07 (0.72–1.6)</td>
<td>11</td>
<td>MP, 30 mg/kg four times</td>
<td>120</td>
<td>120</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Bollaert et al, 1998</td>
<td>41</td>
<td>0.53 (0.26–1.06)</td>
<td>12</td>
<td>HC, 100 mg q8h for 5 d, then 50 mg q8h for 3 d and 25 mg q8h for 3 d for responders</td>
<td>0.9</td>
<td>4.3</td>
<td>11</td>
<td>135</td>
</tr>
<tr>
<td>Briegel et al, 1999</td>
<td>40</td>
<td>0.67 (0.22–2.01)</td>
<td>12</td>
<td>HC, 100 mg, then 0.18 mg/kg/h until shock reversed, then 0.08 mg/kg/h for 6 d, then tapered by 24 mg/d</td>
<td>0.9</td>
<td>6.5</td>
<td>17</td>
<td>Randomized &lt;72</td>
</tr>
<tr>
<td>Annane et al, 2002</td>
<td>299</td>
<td>All, 0.90 (CI, 0.74 to 1.09); nonresponders, 0.83 (CI, 0.66 to 1.04); responders, 1.15 (CI, 0.77 to 1.74)</td>
<td>14.5</td>
<td>HC, 50 mg q6h for 7 d, plus fludrocortisone 50 µg oral tablet qd for 7 d</td>
<td>0.57</td>
<td>4</td>
<td>7</td>
<td>Randomized &lt;8</td>
</tr>
</tbody>
</table>

*HC = hydrocortisone; B = betamethasone; MP = methylprednisolone; DEX = dexamethasone; N/A = data not available. Adapted from Cronin et al.18
†Relative risk for mortality >1 favors control, <1 favors treatment.
‡Quality score is based on the methodologic quality assessment tool described by Cronin et al.18 The maximum score for the 11-part scale is 14.5 points.
§Methylprednisolone equivalents in milligrams per kilogram is based upon milligram to milligram conversions of hydrocortisone by multiplying the hydrocortisone milligram per kilogram dose by 0.2, dexamethasone by multiplying the dexamethasone milligram per kilogram dose by 6, and betamethasone by multiplying the betamethasone milligram per kilogram dose by 4. Average body weight was assumed to be 70 kg when not otherwise stated.
Current Role of Corticosteroid Therapy in Septic Shock

The cumulative pooled results of the prospective, randomized clinical trials published to date fail to confirm or refute a role for corticosteroids as a general class of drugs for septic shock (Fig 1). Historically, suboptimal study design and/or inadequate sample size have prevented establishing definitive conclusions. There are only a few clinical trials that are both large and of high quality: one study is neutral, one study concludes corticosteroids may be harmful, and the most recent study favors corticosteroids for patients with relative adrenal insufficiency (Fig 2). Clearly, there are important differences in the corticosteroid preparations, dosage, and duration of therapy among the various clinical trials. There is now widespread agreement that high-dose, short-course therapy with methylprednisolone or dexamethasone in septic shock is ineffective. In contrast, the prolonged administration of modest doses of hydrocortisone, within the newer paradigm of relative adrenal insufficiency in septic shock, is of primary interest to clinicians today.

This approach to corticosteroid therapy for septic shock appears to be attractive in several ways. Logical mechanistic targets for therapy with low-dose corticosteroids include a state of relative adrenal insufficiency, as well as steroid-responsive adrenergic receptor hyposensitivity. There is consistency in placebo-controlled trials that septic shock patients who receive hydrocortisone are likely to require vasopressor support for a shorter duration of time, and have trends for improved survival. Documented adverse events seem to be infrequent in randomized clinical trials. Finally, hydrocortisone is inexpensive and widely available.

The three randomized clinical trials of hydrocortisone in septic shock are of high quality, with scores of 11.5, 12.0, and 14.5 points (of 14.5 possible points), respectively, utilizing criteria proposed by Cronin and colleagues, but only the recent multicenter trial was adequately powered (Fig 2). Nevertheless, even in these well-designed and well-conducted clinical trials, key issues of sample size, patient selection, concomitant treatment, and statistical analysis have emerged. These issues affect interpretation of the primary results and should influence clinician decision making, including generalization to the broader population of patients with septic shock.

Why not just give hydrocortisone to all patients with septic shock? Although there was a reduction in mortality among hydrocortisone-treated patients who had septic shock with relative adrenal insufficiency (corticotropin nonresponders) in the multicenter clinical trial, patients who responded normally to corticotropin displayed a trend for higher mortality with hydrocortisone therapy (61% vs 53% in the placebo group). There were only 70 corticotropin responders, so the trial was underpowered to detect increased mortality in this arm of the study. In the

**Figure 1.** The relative risk (closed circle) and 95% CIs (bars) for mortality for 12 prospective, randomized, placebo-controlled clinical trials testing a corticosteroid preparation vs placebo. Relative risk < 1.0 favors treatment and > 1.0 favors control. Trials are listed by author, with the most recently published studies toward the top of the Figure. Common relative risk for all clinical trials is uppermost. Modified with permission from Cronin et al. VA = Veterans Administration.
accompanying editorial, Abraham and Evans raise concerns about potential for harm to patients with intact HPA function who receive hydrocortisone, and recommend that "corticosteroids should not be initiated, or must be discontinued, given the possibility of an adverse effect" in such patients.

Testing of HPA axis responsiveness is not a trivial issue. First, normal corticotropin responsiveness is generally more common than the 24% reported in the multicenter trial. For example, in an earlier report from the same investigators, 46% of patients with septic shock were corticotropin responders. Other investigators have reported corticotropin response rates of 25%, 40%, 44%, 59% among patients with septic shock. Thus, nearly half of patients in septic shock are corticotropin responders and probably should not be treated with hydrocortisone, illustrating the importance of corticotropin testing. Why patients with intact HPA axis might have worse outcomes with hydrocortisone therapy is unclear. Typical corticosteroid-related adverse events, such as secondary infections or GI bleeding, were not more common among hydrocortisone-treated patients in the entire cohort of the multicenter trial. Hydrocortisone therapy in septic patients can lead to higher blood glucose levels, which might be associated with worse outcomes as demonstrated in a prospective clinical trial of aggressive insulin therapy for critically ill patients.

A second important issue related to corticotropin stimulation testing is the current scarcity of the synthetic corticotropin analog (α1 corticotropin) preparation used in the United States, cosyntrtopin. The American Society of Health-System Pharmacists currently lists cosyntrtopin on its list of drugs for which there is a nationwide shortage. Finally, there is ongoing debate about optimal testing of the HPA axis function. The low-dose corticotropin stimulation test that uses a dose of 1 µg rather than 250 µg has some support for evaluating HPA axis function, as does the corticotropin releasing hormone stimulation test for secondary adrenal insufficiency; however, there are little data from critically ill patients. Since a small number of corticotropin nonresponders were reported to have a rapid (within 60 min of receiving a 50-mg IV dose of hydrocortisone) improvement in BP response to norepinephrine, one might expect to see hemodynamic improvement after the first dose of hydrocortisone as an early indicator of benefit. The value of these alternative approaches in identifying patients who are likely to benefit from hydrocortisone will require additional research.

There are other issues surrounding the role of hydrocortisone therapy in septic shock. Is it necessary to administer the mineralocorticoid fludrocortisone along with hydrocortisone? Some experts argue that mineralocorticoid replacement is not needed as long as the dose of cortisol exceeds 50 mg/d. Although most investigators randomized patients to hydrocortisone or placebo therapy within 8 h or 72 h of the onset of septic shock, Bollaert and colleagues randomized patients an average of 5 to 6 days after onset of septic shock and demonstrated significantly faster shock reversal (cessation of vasopressors) and a trend for better survival in hydrocortisone group. Finally,
the duration of therapy was 1 week or longer in all three clinical trials but varied widely from 7 to 17 days. Accordingly, optimal time of onset of treatment as well as the duration of treatment with hydrocortisone require additional study.

CONCLUSIONS

It is widely agreed that there is no role for high-dose, short-course corticosteroid therapy in septic shock. The utilization of hydrocortisone in doses of 50 mg IV q6h for 7 days is supported by the results of the multicenter clinical trial, although issues regarding patient selection and statistical analysis confound the results and should be addressed. Importantly, these data suggest there is no benefit—and potential for harm—with hydrocortisone therapy in septic shock patients who have a normal (> 9 μg/dL) increase in plasma cortisol in response to corticotropin testing, making such testing important. Additional research is needed to confirm these clinical trial results, to address alternative tests for HPA axis function in view of cosynotropin shortages, and to refine our understanding of mechanisms by which corticosteroids might work. Finally, it is important to consider that “classical” adrenal insufficiency, diagnosed using traditional criteria, can certainly occur concomitantly with sepsis and requires corticosteroid replacement therapy.

REFERENCES

5 Rothwell PM, Udvadia ZP, Lawler PG. Cortisol response to corticotropin and survival in septic shock. Lancet 1991; 337:582–583
33 Lucas CE, Ledgerwood AM. The cardiopulmonary response...
34 Carlet J. From mega to more reasonable doses of corticosteroids: a decade to recreate hope. Crit Care Med 1999; 27:672–674