Steroids for Septic Shock*
Back From the Dead? (Pro)

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The use of corticosteroids as adjunctive therapy for severe sepsis and septic shock has been a source of controversy for the past 35 years. Despite a wealth of preclinical data supporting both survival and physiologic benefit for early steroid use, the data in human sepsis have been much less convincing. There have even been reports suggesting the potential for harm associated with the administration of early high-dose corticosteroids in patients with severe sepsis and septic shock. Recent trials have reported hemodynamic and survival benefits associated with the use of more physiologic steroid replacement therapy in patients with vasopressor-dependent septic shock. These results coupled with the observation of “relative adrenal insufficiency” in some patients with severe sepsis and septic shock may once again establish a defined role for corticosteroid therapy in the management of severe sepsis and septic shock.

(CHEST 2003; 123:490S–499S)

Key words: corticosteroids; sepsis; septic shock; steroids; vasopressor therapy

Abbreviations: ACTH = adrenocorticotropic hormone; Fio2 = fraction of inspired oxygen; MODS = multiple organ dysfunction syndrome

During the past 35 years, there has been an ongoing controversy concerning the potential benefit of corticosteroid therapy in patients with severe sepsis and septic shock.1–11 This controversy has been fueled by the results of preclinical experimental animal data that have supported a beneficial role for corticosteroids in the treatment of endotoxin or Escherichia coli infusion models of sepsis.12–18 The strength of this preclinical data, coupled with the results of an early clinical trial, helped secure a package insert indication in the late 1970s and early 1980s for methylprednisolone for the management of septic shock.7 Further support for the use of corticosteroids was derived from their successful use in the treatment of diffuse inflammatory processes, such as vasculitis and various collagen vascular diseases.1,3,5,7 Adjuvantive corticosteroid treatment was found to be beneficial in the treatment of meningitis, typhoid fever, and severe Pneumocystis carinii and varicella pneumonia.1,3,5,10 Unfortunately, prospective, randomized, placebo-controlled clinical trials of high-dose corticosteroid use in patients with severe sepsis and septic shock have not supported a therapeutic benefit and have even suggested a potential for harm in some subgroups of septic patients.3,19–26 This discussion will revisit the potential use of corticosteroids in the management of patients with severe sepsis and septic shock in light of some recent data that supports a role for physiologic doses of corticosteroids in patients with severe sepsis and septic shock, as well as patients with the fibroproliferative phase of ARDS.27–31

Potential Benefits of Corticosteroids in Inflammatory States

Corticosteroids are commonly used in a number of inflammatory conditions as the primary pharmacologic agent to suppress the overexuberant pro-inflammatory process. Examples of these inflammatory processes include asthma, collagen vascular diseases, vasculitis, sarcoidosis, and Wegener granulomatosis.31 A consensus conference defined sepsis as the systemic inflammatory response to the presence of a documented infection.32 Septic shock represents a more profound inflammatory response characterized by persistent hypotension despite adequate fluid resuscitation, or the need for vasoactive medication to support an adequate BP coupled with evidence of perfusion abnormality, such as mental status changes, lactic acidosis, or decreased urine output.32 Corticosteroids have been reported to be of value in these inflammatory processes because of their ability to prevent complement activation; inhibit the inducible form of nitric oxide synthase; prevent neutrophil aggregation and adherence induced by endotoxin; decrease the formation of arachidonic acid and platelet activating factor from membrane phospholipids; decrease transcription of tumor necrosis factor and other pro-inflammatory cytokines from activated mononuclear cells; increase transcription of anti-inflammatory cytokines like the interleukin-1 receptor antagonist, and decrease release of adhesion molecules such as intracellular adhesion molecule-1 and vascular cell adhesion molecule-1.1,2,4,5,8,33 Corticosteroids may also increase the number and sensitivity of α- and β-adrenergic receptors and may stabilize the lysosomal membranes to decrease the release of proteolytic enzymes in the inflammatory process.1,2,4,8

Some claim that a state of relative adrenal insufficiency exists in critical illnesses such as severe sepsis and septic shock. A past study34 has demonstrated that in the presence of adrenal insufficiency, there is reduced survival from severe illness. In sepsis, nonsurvivors have been shown to have a persistent pro-inflammatory response that is often accompanied by increased circulating cortisol and corticotropin serum levels. It has been asserted that the high levels of circulating cortisol signifies glucocorticoid resistance.3 The paradoxical relationship between the increased circulating cortisol levels and decreased cortisol effect suggests a decrease in the binding affinity of the glucocorticoid receptor. Meduri and Kanagat37 termed this situation starvation in plenty and emphasized the importance of extended physiologic replacement of corti-
cortisone to overcome this abnormality. The administration of physiologic doses as compared to the suprapharmacologic doses of corticosteroids helps to correct the relative adrenal insufficiency without untoward immunosuppression.4,34 This relative adrenal insufficiency is not always manifested by a reduced cortisol response to corticotropin administration.4,34 Several studies4,34 have demonstrated a lack of correlation between the cortisol response to corticotropin administration and the subsequent beneficial clinical and hemodynamic effects of corticosteroid administration.

**PRECLINICAL DATA IN SUPPORT OF STEROIDS**

The support for the use of high-dose corticosteroids in the treatment of severe sepsis and septic shock was rooted in the dramatic observations of improved hemodynamic parameters and even survival in experimental models of septic shock.12–18 These studies reported on the administration of lethal doses of endotoxin or live *E coli* administered to a variety of experimental animals to reproduce the clinical syndrome of severe sepsis and septic shock. Pretreatment, concomitant treatment, or early posttreatment with corticosteroids was associated with an improvement in the hemodynamic derangements characteristic of this septic model and, importantly, there was also a documented improvement in survival. These observations were found in a variety of animal models, including mice, rats, dogs, sheep, and subhuman primates.12–18 Hollenbach and coworkers15 found that the administration of bolus steroids was as effective as antibiotics in the ability to produce 10-day survival in rats with cecal ligation and perforation as the form of experimental sepsis. Both bolus corticosteroids and antibiotics were able to significantly increase 10-day survival in comparison to placebo control and continuous infusion steroids. Rao and Cavanagh34 found that corticosteroids significantly improved the hemodynamic and cardiovascular performance of subhuman primates that were infused with *E coli* endotoxin. Demling and colleagues14 reported that pretreatment with corticosteroids prevented endotoxin-induced lung injury, while delaying steroids for 1 h was effective in preventing lung injury in four of seven sheep. Brigham and associates16 demonstrated that high doses of methylprednisolone sodium succinate were able to prevent the increase in lung vascular permeability produced by *E coli* endotoxin infusion, if the steroids were administered either prior to the endotoxin infusion or during the hypertensive phase of injury, before the vascular permeability defect was manifest. The preponderance of preclinical data thus supported a potential beneficial role for the use of early, high-dose corticosteroid treatment for severe sepsis and septic shock.

**EARLY CLINICAL STUDIES WITH STEROIDS**

One of the first human randomized, prospective, double-blind placebo-controlled studies of steroid administration as an adjunctive strategy for patients with severe sepsis and septic shock was performed by Bennett and
colleagues\cite{19} and reported in 1963. Using 100 mg of oral hydrocortisone as the initial steroid therapy vs placebo, these investigators were unable to detect a significant survival difference between the treatment and control groups.\cite{20} Neither was there a significant difference in the rate of complications, particularly infectious complications, which was a major concern regarding this form of anti-inflammatory therapy.\cite{6} With the impressive benefits observed in the vast number of experimental animal sepsis trials, it was expected that there would continue to be great interest in further human investigations to determine whether adjunctive corticosteroids were beneficial in the management of humans with severe sepsis and septic shock.

Multiple clinical trials\cite{19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35} were subsequently performed in an attempt to determine if there was a defined benefit associated with the use of corticosteroids in the management of patients with severe sepsis and septic shock. A review\cite{3} critically evaluated a pool of 124 relevant articles on this topic using the techniques of evidence-based medicine and concluded that there was no convincing evidence that high-dose early administration of corticosteroids in patients with severe sepsis and septic shock was beneficial (Fig 1). In fact, there were select subgroups in which this form of therapy was found to result in an increase in mortality.\cite{3} Despite all of these negative trial results, many clinicians continued to use high-dose corticosteroids in the management of patients with severe sepsis and septic shock because of the phenomenal results reported in a study by Schumer\cite{35} in 1978. This study combined a prospective trial with a retrospective analysis contrasting two steroid regimens with a saline solution placebo. The study population consisted of adult surgical patients with septic shock at a Veterans Administration hospital. The patients with septic shock were identified, enrolled, and randomized in a blinded fashion according to a card system. Two steroid preparations were used for this trial, methylprednisolone, 30 mg/kg, and dexamethasone, 3 mg/kg. The study drug was administered via central catheter over 10 to 20 min at study entry and could be repeated, if necessary, in 4 h. One hundred seventy-two consecutive patients were entered into this

![Graph](image1)

**Figure 2.** Evolution of hemodynamic parameters and catecholamine dosage over time. Reprinted with permission from Bollaert et al.\cite{28}
trial over the 8-year study period. The overall mortality in the placebo-treated patients was 38.4%, while the combined steroid-treated patients had a mortality rate of 10.4% (11.6% for methylprednisolone and 9.3% for dexamethasone).35

In a subsequent retrospective analysis of 328 surgical patients with septic shock, the mortality rate of patients who did not receive corticosteroid treatment was 42.5%, while the overall mortality rate in those patients who were treated with high-dose corticosteroids was 14%.35 Again, there was no significant difference between the two steroid preparations evaluated in the study.35 During both phases of the study, the complication rate associated with the use of corticosteroids was similar and was not significantly different from control.35

Notwithstanding such impressive overall results, the Schumer study was heavily criticized.3,6,7,9,11 Among the criticisms of the report were the use of two different corticosteroid preparations, the failure to standardize antibiotic and support regimens, lack of information concerning the adjunctive therapeutic strategies employed in the management of patients, the long follow-up period for mortality reporting, the 8-year duration of the study, and the unusually low mortality rate.7,9,11 There was concern that bias may have played a role in the selection of the patients, given the extremely low mortality rate that was observed in the corticosteroid treatment group. As previously mentioned, there were a number of subsequent multicentered, prospective, randomized, double-blind placebo-controlled trials10–24 that reported no benefit...
associated with the use of early high-dose corticosteroid therapy. In fact, there were some subgroups, such as patients with renal insufficiency, that had a higher mortality rate associated with corticosteroid treatment.21 As a result of these well-conducted clinical trials, it appeared that the practice of using high-dose early corticosteroids for the management of patients with severe sepsis and septic shock was over.

CURRENT CLINICAL EXPERIENCE WITH CORTICOSTEROID TREATMENT

Despite the relative certainty that high-dose corticosteroids were of no therapeutic value in the management of patients with septic shock, there was still interest in evaluating lesser, more physiologic doses of corticosteroids in the inflammatory process of sepsis.36 This endeavor was
likely fueled by the strength of the preclinical data and the rationale that an over-abundant pro-inflammatory response would not likely be beneficial for all patients. Corticosteroids are excellent anti-inflammatory agents and, in more reasonable doses, would not be expected to overly suppress the host defense system and lead to secondary infections. Further support for the potential value of corticosteroids was derived from a number of anecdotal reports of improved lung function and survival in patients with the fibroproliferative phase of ARDS who were treated with corticosteroids.\textsuperscript{4,29} This disorder is a pro-inflammatory response that resembles the mediator and pro-inflammatory response seen in patients with septic shock.\textsuperscript{37,38} In addition, the support for the use of more physiologic corticosteroid therapy in patients with severe sepsis and septic shock was energized by reports of improved survival and/or physiologic function in small, prospective, controlled clinical trials.\textsuperscript{27–29}

Bollaert and colleagues\textsuperscript{28} conducted a prospective randomized, double-blind, placebo-controlled trial to investigate the use of low doses of corticosteroids to improve the hemodynamic status of patients with persistent catecholamine dependence in late septic shock. Forty-two septic shock patients who were still receiving vasopressor therapy after 48 h were randomly assigned to receive 100 mg of hydrocortisone three times a day for 5 days or a matching placebo. The primary end point was shock reversal as defined by a stable systolic arterial BP > 90 mm Hg without vasopressors or fluid resuscitation for ≥24 h along with a blood lactate concentration of < 2 mmol/L. The steroid-treated patients had a greater degree of shock reversal (68% vs 21%, \(p = 0.007\)) and less catecholamine use (Fig 2, 3). The overall 28-day all-cause mortality was 32% in the steroid-treated group and 63% in the placebo group (\(p = 0.045\)) [Fig 3]. In this trial, the main cause of death was progression to multiple organ failure. There was no difference in the adverse effects potentially related to the study medication between the two groups.\textsuperscript{28} The mechanism behind the beneficial response observed in this trial is uncertain, but could be related to the relative adrenal insufficiency or decreased glucocorticoid receptor affinity in the setting of septic shock. Whatever the mechanism, these results certainly supported a reappraisal of the use of low-dose corticosteroids for the management of patients with persistent septic shock.

A subsequent single-center German trial conducted by Briegel and associates\textsuperscript{27} investigated the effect of continuous infusion of stress doses of corticosteroids on the duration of vasopressor therapy in patients with septic shock. This prospective, randomized, double-blind, placebo-controlled trial investigated a regimen of 100 mg of hydrocortisone followed by a constant infusion of 0.18 mg/kg/h over a minimum of 6 days vs placebo in 40 patients with vasopressor-dependent septic shock and a cardiac index of > 4 L/min/m\(^2\). While the majority of both treatment groups reversed their shock state, the steroid treatment was associated with a more rapid reversal and a trend toward earlier resolution of organ dysfunction (Figs 4–6).\textsuperscript{27} In this trial, there were no significant differences in shock reversal or mortality between the two treatment groups.\textsuperscript{27}

Another strong argument in favor of resurrecting corticosteroid treatment for the management of patients with severe sepsis and septic shock came from the use of corticosteroid treatment in patients with the fibroproliferative phase of ARDS. The fibroproliferative phase of

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{sofa_score.png}
\caption{Sepsis-related organ failure assessment (SOFA) score over time. Reprinted with permission from Briegel et al.\textsuperscript{27}}
\end{figure}
ARDS is marked by persistent elevation of pro-inflammatory cytokines in the serum and BAL fluid coupled with clinical manifestations of persistent inflammatory reaction. This persistent pro-inflammatory response is similar to the pathophysiologic manifestations in persistent sepsis. Meduri et al. reported an improvement similar to the pathophysiologic manifestations in persistent decrease in the lung injury score, increase in the PaO2/FIO2 ratio, and a decreased multiple organ dysfunction syndrome (MODS) score with the use of moderate-dose corticosteroid therapy as compared to placebo for patients with the fibroproliferative phase of ARDS. As depicted in Figure 7, over the 10-day primary study end point, there was a significant decrease in the lung injury score, increase in the PaO2/FIO2 ratio of inspired oxygen (FIO2) ratio, and a decrease in the MODS score. Unfortunately, this was a small trial that was further compromised by the crossing over of half of the placebo patients into the steroid treatment group for failure to improve at day 10. Needless to say, this trial has generated a great deal of controversy, and the use of steroids for the fibroproliferative phase of ARDS is currently the focus of a multicenter investigation conducted by the National Institute of Health-sponsored ARDS Network.

Additional support for the potential value of steroid therapy in patients with septic shock was derived from an observation reported by Annane and colleagues that patients with septic shock can be classified according to their basal cortisol level and their ability to increase their basal cortisol level after a short corticotropin stimulation test. They identified 189 consecutive septic shock patients who underwent basal and post-short adrenocorticotropic hormone (ACTH) stimulation cortisol testing. These patients were then followed for 28-day survival. As depicted in Figure 8, the survival of these patients appeared to be related to the combination of both the basal cortisol level and the patients’ ability to increase their serum cortisol > 9 μg/dL after corticotropin stimulation. Those patients who had a basal cortisol level > 34 μg/dL and who were unable to increase their serum cortisol level > 9 μg/dL had the worst prognosis, with a 28-day mortality rate of 82%. Those patients who had a basal cortisol level > 34 μg/dL and were unable to increase their serum cortisol > 9 μg/dL after stimulation had the best prognosis with a 28-day mortality rate of 26%. Those patients who had a basal cortisol level ≤ 34 μg/dL along with a poststimulation increase of ≤ 9 μg/dL or a basal cortisol level > 34 μg/dL and the ability to increase their serum cortisol > 9 μg/dL had a 28-day mortality rate of 67%. These findings support the concept that some patients with severe sepsis and septic shock have “relative” adrenal insufficiency and may benefit from supplemental therapy with corticosteroids.

To test whether the use of adrenal replacement therapy would be beneficial in patients with vasopressor-dependent septic shock and relative adrenal insufficiency as defined by their prior study, Annane and colleagues conducted a multicenter, prospective, randomized, double-blind, parallel-group trial. The primary end point for the trial was the 28-day survival in those patients who did not respond to the short ACTH stimulation test at an increase of their basal cortisol by > 9 μg/dL. All 299 patients enrolled in this trial were adults with well-defined sepsis, and all had an alteration in body temperature, elevated heart rate, hypotension despite adequate volume resuscitation, and/or a requirement for vasopressor therapy, a need for mechanical ventilatory support, an elevated arterial lactate level, and evidence of altered oxygenation status or reduced urine output. The trial compared placebo vs adrenal replacement therapy that consisted of an IV bolus of 50 mg of hydrocortisone q6h combined with 50 μg/d of fludrocortisone orally 7 days. The vast majority of patients enrolled in this trial were adults with well-defined sepsis, and all had an alteration in body temperature, elevated heart rate, hypotension despite adequate volume resuscitation, and/or a requirement for vasopressor therapy, a need for mechanical ventilatory support, an elevated arterial lactate level, and evidence of altered oxygenation status or reduced urine output. The trial compared placebo vs adrenal replacement therapy that consisted of an IV bolus of 50 mg of hydrocortisone q6h combined with 50 μg/d of fludrocortisone orally 7 days. The vast majority of patients enrolled in this trial were found to fit their definition of relative adrenal insufficiency (229 of 299 patients, 76.6%). The use of steroid replacement therapy in this group of vasopressor-dependent septic shock patients with relative adrenal insufficiency was found to have a significant improvement in 28-day survival (47% vs 37%, p = 0.02) and faster withdrawal of vasopressor therapy as compared to placebo treatment. The same significant improvements were not observed in the responders to ACTH or in the overall study population (Table 1).
There were no significant differences in the reported number of adverse events between the two treatment strategies. The authors concluded that 7 days of replacement therapy with physiologic doses of hydrocortisone and fludrocortisone was beneficial in vasopressor-dependent septic shock patients who had relative adrenal insufficiency. Physiologic replacement doses of corticosteroids were evaluated in a single-center, prospective, randomized, double-blind, placebo-controlled trial of 40 septic patients. Patients were randomized to receive either adrenal replacement therapy (5 mg of prednisolone at 6 AM and 2.5 mg of prednisolone at 6 PM) or placebo IV for 10 days. The definition of adrenal insufficiency for this trial was the failure to increase the cortisol level > 20 µg/dL after ACTH stimulation. Using this definition, only 35% of the patients met the criteria for occult adrenal insufficiency. The mortality in the steroid-treated population was 40% as compared to 60% mortality in the standard treatment group. Among those patients with occult adrenal insufficiency, the mortality rate was 40% with replacement therapy and 55.6% with conventional therapy. There were no significant differences noted in survival or adverse events between the two treatment strategies.

These trials lend support to the claim that there may

Table 1—Effect of Physiologic Steroid Replacement vs Placebo in 299 Patients With Vasopressor-Dependent Septic Shock

<table>
<thead>
<tr>
<th>Variables</th>
<th>Placebo</th>
<th>Steroids</th>
<th>Adjusted Odds Ratio (95% Confidence Interval)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonresponders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>115</td>
<td>114</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28-d mortality</td>
<td>73 (63)</td>
<td>60 (53)</td>
<td>0.54 (0.31–0.97)</td>
<td>0.04</td>
</tr>
<tr>
<td>ICU mortality</td>
<td>81 (70)</td>
<td>66 (58)</td>
<td>0.50 (0.28–0.89)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>83 (72)</td>
<td>70 (61)</td>
<td>0.53 (0.29–0.96)</td>
<td>0.04</td>
</tr>
<tr>
<td>1-yr mortality</td>
<td>88 (77)</td>
<td>77 (68)</td>
<td>0.57 (0.31–1.04)</td>
<td>0.07</td>
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<tr>
<td>Responders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>34</td>
<td>36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28-d mortality</td>
<td>18 (53)</td>
<td>22 (61)</td>
<td>0.97 (0.32–2.99)</td>
<td>0.96</td>
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<tr>
<td>ICU mortality</td>
<td>20 (59)</td>
<td>24 (67)</td>
<td>0.99 (0.31–3.16)</td>
<td>0.99</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>20 (59)</td>
<td>25 (69)</td>
<td>1.20 (0.38–3.76)</td>
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<tr>
<td>1-yr mortality</td>
<td>24 (71)</td>
<td>25 (69)</td>
<td>0.70 (0.20–2.40)</td>
<td>0.57</td>
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<tr>
<td>All patients</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>149</td>
<td>150</td>
<td></td>
<td></td>
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<tr>
<td>28-d mortality</td>
<td>91 (61)</td>
<td>82 (55)</td>
<td>0.65 (0.39–1.07)</td>
<td>0.09</td>
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<tr>
<td>ICU mortality</td>
<td>101 (68)</td>
<td>90 (60)</td>
<td>0.61 (0.37–1.02)</td>
<td>0.06</td>
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<tr>
<td>Hospital mortality</td>
<td>103 (69)</td>
<td>95 (63)</td>
<td>0.67 (0.40–1.12)</td>
<td>0.12</td>
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<tr>
<td>1-yr mortality</td>
<td>112 (78)</td>
<td>102 (68)</td>
<td>0.62 (0.36–1.05)</td>
<td>0.08</td>
</tr>
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</table>

*Data are presented as No. (%) unless otherwise indicated. Results are based on patient responses to a short corticotropin test. Using baseline cortisol, cortisol response, McCabe classification, logistic organ dysfunction score, arterial lactate levels, and PaO₂/Fio₂ results for adjustments, analyses were performed with use of logistic models. From Annane et al. 39.
indeed be some clinical benefit to the use of smaller doses of corticosteroids in critically ill septic shock patients. As a result of the potential for smaller doses of corticosteroids to restore the glucocorticoid response and to potentially counter an overabundant pro-inflammatory response, the support for a potential role for corticosteroids in septic shock has steadily grown. Large multicentered, prospective, randomized, placebo-controlled, double-blind trials are now needed to define the risks and benefits of this management strategy. The National Heart, Lung, and Blood Institute ARDS Network is currently evaluating the use of late moderate-dose corticosteroid treatment for the fibroproliferative phase of ARDS. Similar trials are now needed to evaluate the effectiveness of more physiologic steroid therapy in the management of patients with septic shock. Until such trials are completed, we cannot continue to ignore the recent data and conclude that steroids are “dead” insofar as septic shock therapy is concerned. Given the recent observations, there appears to be a beneficial role for the use of physiologic adrenal replacement therapy in septic shock patients who are vasopressor-dependent and demonstrate relative adrenal insufficiency.

**SUMMARY**

While the data appear convincing that suprapharmacologic doses of corticosteroids are not beneficial in the management of a patient with severe sepsis and septic shock, studies suggest that more physiologic doses of corticosteroids may be beneficial in some patients with vasopressor septic shock. Corticosteroid therapy in the patient with persistent septic shock appears to aid in the treatment of the shock state and lead to more rapid reversal of the hemodynamic alterations. As one would expect from the hemodynamic improvement, there was also a benefit seen in overall mortality. Further studies are needed to confirm this observation and to guide us on the best agent, dose, timing, and duration of this therapy. While the use of supraphysiologic doses of corticosteroids in septic shock is certainly “dead,” there appears to be value in the use of more physiologic doses of corticosteroids in the patient with vasopressor-dependent septic shock.

**REFERENCES**

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