Septic shock is the 13th leading cause of death in the United States. The rate of severe sepsis nearly doubled and mortality increased more than 60% during the 10-year period ending in 2003. Systemic inflammatory response syndrome has noninfectious and infectious causes. Noninfectious ones include burns, trauma, severe pancreatitis, and therapy with monoclonal antibodies or immunomodulatory drugs such as interleukin 2. Progression from sepsis syndrome to septic shock is caused by a series of immune responses. As an infectious injury progresses, host activation of the coagulation, immunological, and stress response systems ensues, resulting in tissue hypoperfusion and organ failure. Early studies with small numbers of patients suggest that treatment with low-dose corticosteroids has marked beneficial effects on shock reversal, the immune system, and the hemodynamic profile. Low-dose corticosteroids should only be administered to a subset of patients with septic shock who are unresponsive to fluid replacement and vasopressor therapy. (Critical Care Nurse. 2011;31[6]:16-26)

Sepsis causes marked morbidity and mortality and is a large burden on global health care systems.1 In the United States, from 1993 to 2003, the rate of severe sepsis increased from 25.6% to 43.8% and mortality related to sepsis increased from 30.3% to 49.7%.2 In a study3 of 8251 patients admitted to intensive care units (ICUs) in France, the incidence of septic shock was 8.2 patients per 100 ICU admissions. Septic shock, the most severe manifestation of sepsis, is defined as infection-induced hypotension refractory to fluid replacement that is accompanied by organ dysfunction or hypoperfusion.4 Dellinger et al4 estimated that despite sophisticated antimicrobial therapy and modern intensive care treatment, the 28-day mortality rate for septic shock is 60%. The results of another study5 indicated that septic shock is the most common cause of death in the ICU in the United States and the 13th most common cause of death overall. These data confirm the troubling trend of an increased incidence of sepsis in hospitalized patients.

Corticosteroids have been used to ameliorate septic shock for more than 50 years, but their efficacy has been difficult to prove. In numerous randomized controlled trials before 1990, use of high-dose corticosteroids (HDCs) for septic shock had largely had deleterious effects.6,7 HDC dosages...
with methylprednisolone 30 mg/kg or dexamethasone 3 to 6 mg/kg in divided doses were thought to be beneficial because of the profound anti-inflammatory effect. A landmark multicentered randomized trial of HDC therapy in 381 patients with sepsis was performed in 1987. Patients were randomized to either HDC (30 mg/kg methylprednisolone) or placebo; the mortality rate was significantly higher in patients who received HDC than in patients who received placebo. By 1995 meta-analysis had indicated that treatment with HDC had no overall benefit and that the drugs might produce severe adverse effects due to immunosuppression.

In some randomized controlled trials done since the early 2000s, low-dose corticosteroid (LDC) therapy in septic shock has had beneficial effects. In LDC therapy, the daily dose range is 200 to 300 mg hydrocortisone or its equivalent. However, in the most recent of these studies, a large multinational randomized controlled trial, the investigators discounted the use of LDC in septic shock, again suggesting possible deleterious effects such as superinfection and prolongation of sepsis and septic shock. In this article, we summarize the recent literature on LDC therapy in adult patients with septic shock. We focus on hard outcomes such as 28-day mortality, morbidity, and shock reversal and on effects on the immune response.

**Definitions**

In 1991, the American College of Chest Physicians/Society of Critical Care Medicine agreed on a standard set of definitions of sepsis and its complications to eliminate treatment confusion for researchers and clinicians.

Bone et al defined systemic inflammatory response syndrome (SIRS) as a widespread inflammatory response that includes 2 or more of the following physiological responses: temperature greater than 38°C or less than 36°C, heart rate greater than 90/min, respirations greater than 20/min or hyperventilation (Paco₂ <32 mm Hg), and white blood cell count greater than 12 000/µL or less than 4000/µL or the presence of immature neutrophils.

Sepsis occurs when SIRS is associated with a confirmed infectious process. Sepsis is the systemic response of the host to the presence of infection. Clinical distinction between sepsis and SIRS is important because noninfectious causes of SIRS, such as burns, trauma, pancreatitis, and immunomodulatory therapy with drugs like interleukin (IL) 2, do not warrant antimicrobial therapy. The development of sepsis is largely affected by the ability of the host to respond to the invading organism or pathogen. Early activation of the host’s response determines the severity and outcome of the inflammatory process.

The progression from sepsis to septic shock occurs as the host’s immune response intensifies. The illness evolves from early SIRS/sepsis, to sepsis with organ dysfunction associated with hypoperfusion or hypotension (severe sepsis) and ultimately to sepsis with hypotension resistant to fluid replacement and accompanied by worsening systemic signs such as lactic acidosis, oliguria, and changes in mental status (septic shock).

**Current Practice Guidelines**

In 2004, the Surviving Sepsis Campaign sponsored by the Society for Critical Care Medicine provided the first standardized guidelines for management of severe sepsis and septic shock. The administration of LDC was then recommended (grade 1C level recommendation: strongly effective) for patients experiencing vasopressor-dependent septic shock, regardless of adrenal function. However, the guidelines on the use of LDC were changed in the 2008 revision to downgrade this recommendation (grade 2B: possibly effective). According to the 2008 guidelines, LDC should only be considered for patients in septic shock when hypotension responds

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poorly to fluid replacement and high-dose vasopressors. These changes to the guidelines signify the ongoing controversy on the efficacy of LDC in septic shock and contribute to the uncertainty of clinicians in using LDCs in practice.

Physiological Rationale for the Use of LDC in Sepsis

After sepsis occurs and progresses, activation of the host’s coagulation, immunological, and stress response systems ensues. In the immune inflammatory response, macrophages are stimulated by toxins released from gram-negative or gram-positive bacteria to produce proinflammatory cytokines such as tumor necrosis factor, IL-1, IL-6, IL-8, and granulocyte colony-stimulating factor. This cascade affects cellular perfusion, impairs oxygen utilization, increases apoptosis, and deregulates the circulatory system by increasing vasodilatation via increased production of nitric oxide. The coagulation cascade is triggered by the activation of proinflammatory cytokines. Depletion of endogenous anticoagulant molecules that affect the vascular endothelium, platelets, and white blood cells often leads to an overexaggerated procoagulant state and the formation of microemboli.

As shown in the Figure, the stress response mediated by the hypothalamic-pituitary-adrenal axis is evoked by the action of cytokines. This initial stimulus is processed in the hypothalamus, resulting in the release of corticotropin-releasing hormone. The pituitary gland then releases corticotropin, which stimulates the adrenal glands to release cortisol. Cortisol is a glucocorticoid critical for homeostatic regulation and adaptation when the body is under stress. Stress states such as septic shock cause the corticotropin levels to increase, but the adrenal glands may be unable to produce sufficient cortisol to meet the added stress needs. Administration of corticosteroids in septic shock is thought to make up this cortisol deficit to produce a beneficial effect on the immune and inflammatory responses through white blood cells, cytokines, and production of nitric oxide. This understanding has formed the theoretical basis for the randomized controlled trials on the effects of LDC conducted from 1999 onward.

Annane et al reported the natural history of endogenous cortisol levels and adrenal responsiveness during septic shock in 2000. They found that cortisol levels measured early during septic shock and the increase in cortisol induced in a short corticotropin stimulation test (0.25 mg tetracosactrin) were significantly correlated with 28-day mortality. High basal cortisol levels (>34 µg/dL) plus small increases after stimulation (<9 µg/dL) were predictive of high mortality (82%), whereas low initial cortisol levels (≤34 µg/dL) plus strong increases after stimulation (>9 µg/dL) were predictive of much lower mortality (28%). These data provided an important foundation for later studies that we critique in the following sections.

Organization of Review and Quality of References

The literature search involved a computerized search of all randomized controlled trials, meta-analyses, and evidence-based reviews found in
PubMed, MEDLINE, and CINHAL (1995-2008) databases when the following specific search terms were used: septic shock, severe sepsis, and low-dose corticosteroids, in combination with intensive care, mortality, adrenal insufficiency, and adult patients in septic shock. The search was limited to English language articles and yielded 11 randomized controlled trials, 1 retrospective analysis, and 4 evidence-based reviews published from 1999 to 2008. The 5 randomized controlled trials and 1 retrospective analysis reviewed here were chosen for their similarity of outcome criteria and quality of study design. Data on adrenal insufficiency and the immunological response in patients experiencing septic shock and who received LDC therapy were included to contrast with conflicting data published previously.

Critical Review of Literature

Briegel and Colleagues, 1999

Briegel et al first investigated the effects of LDC (hydrocortisone) in septic shock. The investigators designed a prospective, randomized double-blind, single-center study and collected data from 1993 through 1996. The primary outcome measure was time to shock reversal. Shock reversal was defined as cessation of the need for vasopressor support. Secondary end points were the evolution of hemodynamic parameters and multiple organ dysfunction syndrome.

The study population was obtained from a consecutive sample of patients with septic shock admitted to a multidisciplinary ICU. The diagnosis of septic shock conformed to the definition provided by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee.

A total of 40 patients were randomized to receive either LDC (hydrocortisone) or placebo (physiological saline). LDC therapy was initiated with a loading dose of 100 mg (hydrocortisone) and then maintained by an intravenous infusion dosage of 0.18 mg/kg per hour. If reversal of shock was achieved, the infusion dose of hydrocortisone was decreased to half, but treatment was continued for an additional 6 days. All patients were managed by conventional therapy that included antimicrobial therapy, mechanical ventilation, and hemofiltration.

Time to shock reversal was significantly decreased in the patients given LDC therapy. The median time to vasopressor cessation was 2 days in the LDC group and 7 days in the placebo group ($P = .005$). Reversal of the shock state occurred in 18 of 20 patients in the LDC group and 16 of 20 in the placebo group. The LDC group showed slightly improved hemodynamic parameters with increased mean arterial pressure and cardiac index, but the differences between the 2 groups were not significant.

Briegel et al concluded that LDC reduced the median time to shock reversal. Baseline characteristics and treatment strategies were similar between groups, a situation that increased the ability to generalize these results. However, the study was limited by the small sample size and suggested the need for more definitive larger studies.

Annane and Colleagues, 2002

Annane et al organized a multicenter, placebo-controlled, randomized trial in 19 ICUs in France from October 1995 to February 1999. In this landmark study, Annane et al hypothesized that patients in septic shock with relative adrenal insufficiency (nonresponders) would benefit from LDC therapy. The purpose of the study was to determine if the primary outcome measure of 28-day mortality was changed by the administration of LDC in adult patients with septic shock and relative adrenal insufficiency. Secondary outcomes included time to vasopressor withdrawal and shock reversal.

A total of 299 patients who met the usual criteria for septic shock were randomized within 8 hours of the onset of septic shock to receive hydrocortisone intravenously every 6 hours as a 50-mg bolus plus 1 tablet (50 µg) of fludrocortisone via nasogastric tube for 7 days (n = 150) or placebo (n = 149). The following inclusion criteria for septic shock were used: (1) documented site (or at least strong suspicion) of infection, culture of a normally sterile body fluid positive for an infectious organism or Gram stain of the fluid showed organisms, clinical focus of infection (eg, fecal peritonitis), wound with purulent discharge, pneumonia or other clinical evidence of systemic infection; (2) temperature higher than 38.3°C or lower than 35.6°C; (3) heart rate greater than 90/min; (4) systolic arterial pressure less than 90 mm Hg for at least 1 hour despite adequate fluid replacement and more than 5 µg/kg of body weight of dopamine or current treatment with epinephrine or norepinephrine; (5) urinary output less than 0.5 mL/kg of body weight for at least 1 hour or ratio of PaO2 to the fraction of inspired oxygen less than 280; (6) arterial blood lactate levels greater than 2 mmol/L; and
A marked weakness was the use of both a glucocorticoid and a mineralcorticoid, making distinctions between the effects of each drug difficult. The results of this study provided the greatest support for the recommendations of the Surviving Sepsis Campaign in 2004, because it was the largest study to date on LDC in patients with septic shock. However, the study findings have yet to be reproduced.

**Keh and Colleagues, 2003**

Keh et al.²⁰ performed a randomized, double-blind, placebo-controlled crossover trial to investigate the effects of LDC on immunological parameters (primary outcome) and hemodynamic parameters (secondary outcome). Addition of the crossover element improved the strength of this study because each patient received the intervention and served as his or her own control.

A total of 40 patients with the confirmed standardized diagnosis of septic shock, according to the Society of Critical Care Medicine guidelines, were enrolled and were divided into 2 groups. The first group, HC-1 (n=20), received hydrocortisone as a 100-mg intravenous bolus followed by an infusion of 10 mg/h for 3 days. This treatment was followed by a maintenance dose of isotonic saline for days 4 through 6. The second group, HC-2 (n=20), received hydrocortisone as a 100-mg intravenous bolus followed by an infusion of 10 mg/h for 3 days. This treatment was followed by a maintenance dose of isotonic saline for days 4 through 6. The immune response was evaluated by measuring the serum levels of cortisol, IL-4, IL-6, IL-8, IL-10, IL-12, E-selectin, soluble tumor necrosis factors I and II, and nitrite/nitrate. Immune cellular measures included leukocyte differentiation, expression of HLA-DR on monocytes and of CD11b and CD64 on granulocytes, and in vitro determination of phagocytosis and respiratory bursts in monocytes and granulocytes. Secondary outcomes included thermodilution cardiac output, mean arterial pressure, heart rate, central venous pressure, and pulmonary artery capillary wedge pressure. Systemic and pulmonary vascular resistances and cardiac index were calculated.

Plasma cortisol levels increased 5-fold in both groups after administration of hydrocortisone and were associated with stabilization of hemodynamic parameters (mean arterial pressure, systemic vascular resistance, heart rate, and cardiac index) in both groups. On day 3, a total of 14 of 20 patients receiving hydrocortisone early were no longer receiving norepinephrine infusions compared with only 6 of 20 patients yet to receive hydrocortisone (P=.03). After crossover, only 12 of 20 patients in whom hydrocortisone treatment was withdrawn were weaned from norepinephrine at 6 days, whereas 17 of 20 patients receiving hydrocortisone late were weaned. A total of 6 of 20 patients in the early hydrocortisone treatment group required norepinephrine again after hydrocortisone withdrawal.

These hemodynamic effects correlated with serum measurements of mediators associated with sepsis. Plasma concentrations of nitrite/nitrate were reduced during hydrocortisone treatment and coincided with a reduced requirement for norepinephrine. After 24 hours of hydrocortisone administration, concentrations of IL-6, IL-8, IL-10, and
soluble tumor necrosis factors I and II were significantly lower in the HC-1 group than in the HC-2 group ($P < .01$). Serum levels of IL-12 and interferon gamma were increased. The serum concentration of IL-4 remained unchanged, and the immune response associated with type 1 T helper cells was not inhibited. Infusion of hydrocortisone was associated with a decrease in the levels of IL-10 and tumor necrosis factor I and II, and then the concentrations rebounded to higher levels when the hydrocortisone infusion was stopped on day 3 ($P < .01$).

This study indicated an improvement in hemodynamic parameters, compensatory anti-inflammatory response with inhibited systemic inflammation, and the maintenance of the immune response mediated by type 1 helper T cells. Hydrocortisone had a significant effect on both vascular tone and hemodynamic parameters, although the specific function of the hypothalamic-pituitary-adrenal axis was not addressed in this study.

**Oppert and Colleagues, 2005**

Oppert et al performed a single-center randomized controlled trial of patients with septic shock to investigate the effects of LDC on shock reversal and changes in the cytokine profile. The results complement the findings of earlier investigators who postulated that the benefit of LDC is related to impaired endogenous adrenal function in sepsis.

A total of 41 patients were enrolled in the study and received either hydrocortisone ($n=18$) or placebo ($n=23$). Patients were randomly assigned to the 2 groups and had a cortisol stimulation test. After the test, LDC or placebo was administered. Patients in the experimental group were given a 50-mg bolus of hydrocortisone and then a continuous infusion of hydrocortisone at the rate of 0.18 mg/kg per hour. Patients were followed up for the cessation of need for vasopressor support (>1 hour), and then the therapeutic infusion (hydrocortisone or saline) was tapered off until discontinuation. Patients were followed up for 28 days thereafter. Blood samples were obtained for measurements of cytokines, C-reactive protein, and cortisol. Cytokines included IL-6 and IL-10, and concentrations were determined on the day of enrollment and then on days 1, 3, 5, 7, and 14. Blood samples from 8 healthy volunteers (controls) were assayed to establish baseline levels of the cytokines.

Shock reversal occurred earlier in the hydrocortisone group than in the placebo group (53 hours vs 120 hours; $P < .02$). At day 2, a total of 9 patients in the hydrocortisone group and 19 in the placebo group were still in shock, requiring vasopressors ($P = .04$). IL-6 levels for both groups were elevated at baseline, but in the hydrocortisone group, the levels declined rapidly to the normal range from days 1 to 5 and were significantly lower overall ($P < .001$). On the basis of the cortisol stimulation test, each patient was classified as either a responder or a nonresponder. Although the results of the stimulation test suggested a beneficial effect of hydrocortisone on shock reversal in nonresponders ($P = .06$), analysis of inflammatory mediators did not show a difference in reduction of cytokine levels between responders and nonresponders.

The results of the study supported the hypothesis that LDC improved shock reversal, and confirmed that some patients in septic shock have relative adrenal insufficiency. Evidence that LDC affects cytokines or the inflammatory response was minimal, although the decrease in IL-6 levels did correlate with improvement in hemodynamic parameters.

**Raurich and Colleagues, 2007**

The studies by Briegel et al., Annane et al., Keh et al., and Oppert et al. provide moderately strong support for the use of LDC in patients with septic shock. The study by Raurich et al. provides a contrasting view. Raurich et al. performed a retrospective, case-controlled analysis in 203 patients with septic shock. A total of 124 patients had received LDC; 79 had not. Baseline characteristics of the patients revealed no significant differences between the 2 groups. Time to shock reversal was defined as the time from initiation of norepinephrine to cessation of the drug for at least 24 hours.

In an attempt to control for bias between groups, the investigators developed a propensity score for the patients who received LDC. The score was calculated by using a logistic regression model and all baseline data. Time to cessation of vasopressor therapy in the LDC group was analyzed by using Kaplan-Meier curves and log-rank tests for median time with an adjusted Cox regression model including propensity scores. In-hospital mortality was analyzed by using logistic regression to include the propensity score, reported with odds ratios and corresponding confidence intervals.

The primary finding was that LDC did not affect duration of shock...
or mortality in patients with septic shock. The amount of norepinephrine used was notably higher in the LDC group than in the non-LDC group (P<.001). Median time to vasopressor cessation was 11 days in the LDC group and 7 days in the control group (P=.16). Differences between groups in time to shock reversal or mortality were not significant.

These results contradict the findings of previous investigators but must be interpreted with caution because of the retrospective design of the study.

Sprung and Colleagues, 2008

The final study is the largest and most recently published one at the time of our review. Sprung et al10 performed the Corticosteroid Therapy of Septic Shock (CORTICUS) study: a multicentered double-blind, placebo-controlled, randomized trial. The purpose of the study was to evaluate the efficacy of LDC in a broad population of patients with septic shock. The investigators acknowledged the increased use of LDC for septic shock because of the 2004 guidelines of the Surviving Sepsis Campaign. However, they pointed out that beneficial outcomes had only been reported in patients with septic shock who were nonresponders to a short corticotropin test and who remained hypotensive after aggressive fluid replacement and vasopressor treatment.

The CORTICUS trial was organized in 52 ICUs in 9 countries. The primary outcome was 28-day mortality in patients with septic shock who were nonresponders to a short cortisol stimulation test. Secondary outcomes were 28-day mortality in responders, overall mortality, reversal of shock, durations of ICU and hospital stay, and the development of new sepsis due to superinfections.

A consecutive sample of patients more than 18 years old were prospectively enrolled in the trial. A total of 499 patients were randomized to hydrocortisone (n=251) or placebo (n=248) groups. Hydrocortisone was given in 50-mg intravenous boluses every 6 hours and then tapered off during the course of 11 days. Shock reversal was defined as systolic blood pressure greater than 90 mm Hg without vasopressor use for 24 hours. Nonresponders were patients who had an increase in plasma level of cortisol less than 9 µg/dL after corticotropin stimulation of the adrenal glands.

Power analysis indicated that 800 patients were needed to achieve 80% power to detect a mortality difference of 10%; therefore, this study may be considered underpowered. No significant differences in 28-day mortality were found between the LDC group and the placebo group among either nonresponders (39.2% in the LDC group vs 36.1% in the placebo group) or responders (28.8% vs 28.7%). Shock reversal was achieved more quickly and earlier among patients in the LDC group than in the placebo group regardless of adrenal function (P=.001); however, the proportion of patients in whom shock reversal was achieved was similar between the 2 groups. The time to shock reversal was 3.3 days in the LDC group and 5.8 days in the placebo group. Unfortunately, an increased risk of superinfection and evidence of new sepsis or septic shock occurred in the LDC group (combined odds ratio, 1.37; 95% CI, 1.05-1.79).

This study was the largest randomized controlled trial in which LDC in septic shock was examined in relation to adrenal insufficiency. Sprung et al10 acknowledged the lack of statistically significant findings and speculated that their use of an expanded enrollment time frame of 72 hours might have affected the results. Post hoc analyses also revealed increased mortality for both responders and nonresponders who received etomidate (P=.03). Because etomidate can suppress the adrenal response in critically ill patients, these patients should have been excluded from the study. A study21 completed after the CORTICUS trial concluded that even a single bolus dose of etomidate in patients with septic shock could result in an inadequate response to corticotropin and was associated with increased mortality.

Discussion

The purpose of our review was to examine the best existing studies in which investigators evaluated LDC therapy in patients with septic shock. The studies that were critiqued are summarized in the Table. The primary outcome was shock reversal in 3 studies, 28-day mortality in 2 studies, and an analysis of the inflammatory immune response in 1 study. Cytokine profile was examined in 1 study as a secondary end point, and shock reversal was used in 2 studies as a secondary outcome.

LDC in Shock Reversal

In the study by Briegel et al,18 shock reversal was significantly reduced: 2 days in the LDC group vs 7 days in the placebo group. Oppert et al21 also reported enhanced shock
reversal, but only in the patients with concurrent adrenal insufficiency (nonresponders). The similarity of findings on shock reversal was encouraging but also raised the question of which patients in septic shock benefit from LDC therapy: responders or nonresponders? However, these 2 studies were underpowered and somewhat outdated in the supportive treatments used at the time. In these 2 small studies, Briegel et al and Oppert et al concluded that LDC appeared to be indicated for patients in septic shock but acknowledged that larger studies were warranted to confirm the results.

In 2 larger studies, Annane et al and Sprung et al (CORTICUS trial) used shock reversal as secondary end points. These investigators used a standardized low-dose corticotropin test to evaluate adrenal function. Nonresponders differed significantly from responders in shock reversal in the study by Annane et al, whereas in the CORTICUS trial, shock reversal was achieved earlier in the LDC group than in the placebo group regardless of adrenal function. Clearly, this supraphysiological stimulation of the adrenal gland is not indicated in all patients. The results of the retrospective study by Raurich et al did not indicate a benefit in shock reversal with LDC treatment, but the study was limited by its retrospective nature. If the results of Raurich et al are excluded, then all 4 randomized controlled trials in which shock reversal was analyzed indicated that LDC appears to have a significant effect on the reversal of shock.

The results of the study by Keh et al also supported the use of LDC treatment in patients with septic shock, as indicated by beneficial effects on hemodynamic parameters, prevention of the compensatory inflammatory response, and the maintenance of the immune response due to a reduction in the production of nitrite/nitrate. That study could have been improved if information on the hypothalamic-pituitary-adrenal axis in septic shock had been included. The primary strength was the crossover design, enabling all subjects to receive the intervention.

Oppert et al also evaluated the cytokine profile, as a secondary end point, and found that treatment with LDC was associated with decreased levels of proinflammatory cytokines in patients in septic shock, suggesting immunomodulatory effects of LDC therapy. The studies by Oppert et al and Keh et al were significantly underpowered, and additional studies on the inflammatory response are needed to improve our understanding of the basic biology of sepsis.

### Table: Summary of major trials of corticosteroids in septic shock

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcomes</th>
<th>Study design</th>
<th>Study size</th>
<th>Interventions</th>
</tr>
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</table>
| Briegel et al, 1999 | Primary: Shock reversal, defined as cessation of vasopressor support  
Secondary: Hemodynamic parameters, multiple organ dysfunction syndrome | Single-center randomized controlled trial | 20/20      | Randomly assigned hydrocortisone (loading dose plus infusion) vs placebo for 6 days |
| Annane et al, 2002  | Primary: 28-day mortality in patients with relative adrenal insufficiency  
Secondary: Shock reversal, vasopressor withdrawal | Multicenter randomized controlled trial   | 151/149    | Randomly assigned hydrocortisone/fludrocortisone vs placebo for 7 days       |
| Keh et al, 2003     | Primary: Low-dose corticosteroids’ effects on the immunological profile  
Secondary: Hemodynamic parameters | Randomized controlled trial with crossover | 20/20      | Initial loading dose of hydrocortisone and intravenous infusion for 3 days |
| Oppert et al, 2005  | Primary: Shock reversal  
Secondary: Cytokine profile | Single-center randomized controlled trial | 18/23      | Randomly assigned bolus plus infusion of hydrocortisone vs placebo           |
| Raurich et al, 2007 | Primary: Shock reversal, mortality | Retrospective, case-controlled analysis | 124/79     | Hydrocortisone every 6 hours (72/124) plus fludrocortisone (52/124) for 7 days vs none |
| Sprung et al (CORTICUS), 2008 | Primary: 28-day mortality in nonresponders  
Secondary: 28-day mortality in responders, shock reversal, overall mortality rate, intensive care unit and hospital duration of stay | Multicenter randomized controlled trial | 251/248    | Hydrocortisone bolus every 6 hours for 6 days, then tapered over 5 days vs placebo |
LDC and Mortality

The primary outcome in the CORTICUS trial and the study by Annane et al was 28-day mortality. These 2 studies offer the most important information on LDC in patients with septic shock and are the ones most referenced in evidence-based recommendations. In the study by Annane et al, LDC treatment in patients with septic shock reduced short-term (28 day) and long-term mortality. Patients who improved in this study were primarily adrenal insufficient (nonresponders), and therapy was recommended solely for this subset of patients in septic shock. In contrast, in the CORTICUS trial, LDC in patients with septic shock was not efficacious; neither responders nor nonresponders had any improvement in survival. The results of the CORTICUS trial have caused clinicians to reconsider the use of LDC in patients with septic shock.

Many factors may contribute to these divergent findings. Patients were more severely ill in the study by Annane et al than in the CORTICUS trial; overall mortality was near 60% in the study by Annane et al and 35% in the CORTICUS trial. Furthermore, implementation and discontinuance of LDC differed markedly in the 2 studies. The inclusion process also differed; Annane et al used an 8-hour window of septic shock, whereas the CORTICUS investigators allowed 72 hours. The CORTICUS investigators gradually tapered the course of LDC, whereas Annane et al continued the same level of therapy for 7 days. Furthermore, Annane et al also administered fludrocortisone, a mineralocorticoid, which was not administered in the CORTICUS trial. So despite similarity in the design, marked differences exist between these 2 studies in general patient characteristics, severity of sepsis, overall mortality, and treatment model. These study differences suggest that patients who more closely resemble those enrolled in the study by Annane et al (sicker, nonresponders) represent a group of patients with septic shock to whom LDC should be administered.

Important additional findings of the CORTICUS trial attributed to LDC treatment included increased incidence of new episodes of sepsis or septic shock, uncontrolled hyperglycemia, and superinfection. The results of the CORTICUS trial also raised concern about the prognostic importance of adrenal insufficiency in patients with septic shock; its importance was not well supported.

Conclusion

The debate on LDC therapy and impairment of the hypothalamic-pituitary-adrenal axis in septic shock has not been resolved. Despite standardized sepsis guidelines and early antimicrobial therapy, mortality related to septic shock remains unacceptably high. Gaps in our understanding of sepsis include a definitive understanding of the relevance of relative adrenal insufficiency in patients with septic shock and the association between superinfection and LDC therapy. The published randomized controlled trials on LDC therapy in patients with septic shock were underpowered, a situation that limits the ability to provide clear evidence-based recommendations.

The finding most supported by these studies is that corticosteroids may accelerate shock reversal. Clinicians must be mindful, however, that shock reversal is not predictive of mortality. Current practice guidelines published by the 2008 Surviving Sepsis Campaign have retained the recommendation to use LDC for patients in vasopressor-dependent septic shock regardless of adrenal function. Clinicians should continue to follow evidence-based guidelines until additional studies reproduce findings of the CORTICUS trial.

At this time, LDC should be administered to a subset of patients who are in septic shock and are unresponsive to fluid replacement and vasopressor therapy. However, clinicians must be familiar with the results of the CORTICUS trial and the associated risks of LDC therapy and the potential for superinfection. Clinicians should also be cognizant of the adverse effect of administering LDC and etomidate. A recent study revealed greater mortality in patients with septic shock receiving LDC therapy who were given etomidate. This increase in mortality most likely is associated with the depression of the hypothalamic-pituitary-adrenal axis caused by the etomidate.

When considering the option of using LDC in patients with severe sepsis or septic shock, clinicians should examine all these secondary risks before starting LDC therapy. Patients should be evaluated on a case-by-case basis for LDC therapy, and integration of any new evidence-based findings should be evaluated as the findings become available.

Relevance for Nursing Clinical Practice

The severity of illness for patients with septic shock is well established. However, use of steroids in patients with septic shock...
Surviving Sepsis Campaign International guidelines in 2008, patients in sepsis with septic shock refractory to aggressive fluid replacement and vasopressor therapy should receive LCD (hydrocortisone). The dosage may be up to 300 mg/d intravenously. Doses of hydrocortisone greater than 300 mg/d may be harmful. Because of the essentially unchanged mortality rate for septic shock since the early 2000s, treatments such as LCD therapy will continue to be controversial. Critical care nurses who care for patients with septic shock should review current evidence-based literature and hold clinicians to these standards of practice.

Financial Disclosures
None reported.

References
1. What was the increase in mortality related to severe sepsis during the 10-year period ending in 2003?
   a. More than 30%  c. More than 50%
   b. More than 40%  d. More than 60%

2. What was the incidence of septic shock per 100 patients admitted to intensive care units (ICUs) in France?
   a. 2.2  c. 6.2
   b. 4.2  d. 8.2

3. Which is correct about septic shock?
   a. It is defined as hypotension refractory to fluid resuscitation.
   b. The estimated 28-day mortality rate is 15%.
   c. It is the most common cause of death in ICUs in the United States.
   d. Corticosteroids have been used to treat septic shock for less than 10 years.

4. What did numerous randomized controlled trials before 2000 demonstrate about the use of high-dose corticosteroids (HDC) to treat septic shock?
   a. HDCs had largely deleterious effects.
   b. The use of HDCs resulted in improved survival.
   c. Patients receiving HDCs did not experience immunosuppression.
   d. Treatment with HDCs demonstrated an overall benefit.

5. What dose of methylprednisolone was considered HDC therapy in clinical trials?
   a. 10 mg/kg  c. 20 mg/kg
   b. 15 mg/kg  d. 30 mg/kg

6. What cause of systemic inflammatory response syndrome warrants treatment with antimicrobial therapy?
   a. Burn injury  c. Pancreatitis
   b. Intra-abdominal abscess  d. Interleukin 2 drug therapy

7. What is defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion?
   a. Systemic inflammatory response syndrome
   b. Early sepsis
   c. Severe sepsis
   d. Septic shock

8. What do proinflammatory cytokines cause in the immune inflammatory response?
   a. Impaired oxygen utilization
   b. Decreased apoptosis
   c. Decreased vasodilatation
   d. Decreased nitric oxide production

9. What hormone is released by the pituitary gland during stress states such as septic shock?
   a. Corticotropin-releasing hormone
   b. Cortisol
   c. Corticotropin
   d. Norepinephrine

10. What finding is most supported by the studies evaluating LDC therapy in patients with septic shock?
    a. LDC therapy improves hemodynamic parameters.
    b. LDC therapy benefits patients with relative adrenal insufficiency.
    c. LDC therapy may accelerate shock reversal.
    d. LDC therapy reduces short- and long-term mortality.

11. What is a 2008 Surviving Sepsis Campaign recommendation about corticosteroid administration in adults with septic shock?
    a. Hydrocortisone should be considered when hypotension responds poorly to adequate fluid resuscitation and vasopressors.
    b. Corticotropin stimulation testing is recommended to identify patients who should receive corticosteroids.
    c. Corticosteroid therapy is recommended to treat sepsis in the absence of shock.
    d. Hydrocortisone is recommended for all patients receiving hydrocortisone.

12. What drug has been shown to cause greater mortality in patients with septic shock receiving LDC therapy by suppressing the hypothalamic-pituitary-adrenal axis?
    a. Succinylcholine
    b. Etomidate
    c. Ketamine
    d. Propofol

Test answers: Mark only one box for your answer to each question. You may photocopy this form.

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