REVIEW

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# Use of corticosteroids in the sepsis syndrome: What do we know now?

## ABSTRACT

Several lines of evidence support the use of corticosteroids as adjunctive therapy for sepsis. In human trials, high-dose, short-course corticosteroid therapy for sepsis has not shown benefit, but prolonged use of low doses has shown benefit in patients with vasopressor-dependent septic shock. The Corticosteroid Therapy of Septic Shock (CORTICUS) trial is addressing the remaining questions regarding the ideal target population for corticosteroid therapy, as well as the best definition of relative adrenal insufficiency in the critically ill.

## KEY POINTS

There are no data to support the use of corticosteroids in septic patients who are hemodynamically stable, ie, without shock.

Short courses of high-dose steroids (eg, hydrocortisone > 300 mg/day) should not be used for septic shock. Hydrocortisone can be given intravenously either as 50 mg every 6 hours for at least 7 days or as a continuous infusion of 10 mg/hour following a loading dose of 50 to 100 mg over 20 to 30 minutes.

An adrenocorticotropic hormone (ACTH) stimulation test may not be necessary to determine who should receive glucocorticoid therapy.

Hydrocortisone should be tapered over at least a few days to prevent rebound hypotension.

SHOULD PATIENTS with sepsis syndrome receive corticosteroid therapy? Although there is a physiologic rationale for the use of corticosteroids in sepsis, there are also safety concerns. To date, clinical trials have been ambiguous. Use of high-dose corticosteroids does not seem beneficial, while trials of lower-dose corticosteroids seem to show benefit in some patients, but there are many unanswered questions.

A definitive trial is under way, which may provide clearer answers. Pending the results of this trial, this article analyzes the evidence to date and gives the author's personal recommendations for the use of corticosteroids in patients with sepsis.

## MORTALITY RATE IS HIGH

Severe sepsis, defined as a systemic inflammatory response syndrome due to infection with accompanying end-organ dysfunction, occurs in approximately 750,000 patients in the United States each year. Despite advances in critical care, the mortality rate remains just under 30%.[1]

Only one adjuvant therapy, drotrecogin alfa (activated) (Xigris), a recombinant form of human activated protein C, is approved for treating severe sepsis. This therapy is indicated only for the sickest patients, is very expensive, and can cause life-threatening bleeding.

## RATIONALE FOR USING CORTICOSTEROIDS

### Corticosteroids reduce inflammation

The initial pathophysiologic mechanism of the organ failure that occurs in severe sepsis is

driven by a systemic inflammatory response.

Components of the outer membrane of both gram-positive and gram-negative organisms can bind to the CD14 receptors of monocytes and, via transmembrane Toll-like receptors, signal the cells to produce nuclear factor kappa B (NF-kappa B) and subsequently the inflammatory cytokines tumor necrosis factor (TNF)-alpha and interleukin-1 (IL-1).[2,3]

Both of these cytokines have a direct toxic effect on tissues. In addition, they activate phospholipase $A_2$, leading to increased concentrations of platelet-activating factor, increased nitric oxide synthase activity, increased tissue infiltration by neutrophils, and increased neutrophil activity.[4,5] These cytokines also trigger the coagulation cascade by causing the expression of tissue factor on the surface of endothelial cells and monocytes.[6]

Corticosteroids could reduce the exaggerated inflammatory response in sepsis through numerous mechanisms:

- Corticosteroids inactivate the NF-kappa B complex, thus decreasing the production of inflammatory cytokines.[7]
- An inhibitor to phospholipase $A_2$ is produced in the presence of glucocorticoids, leading to decreased formation of arachidonic acid and platelet-activating factor.[8]
- Glucocorticoids inhibit complement activation and neutrophil aggregation.[9]
- Glucocorticoids normalize the production of macrophage migratory inhibitory factor, a substance that is synergistic with endotoxin in inducing the production of inflammatory cytokines.[10]
- Corticosteroids inhibit the release of toxic enzymes such as lysozyme and superoxide from neutrophils.[11]
- In clinical trials in humans with sepsis and in acute respiratory distress syndrome, corticosteroid therapy attenuated components of the systemic inflammatory response as well as inflammatory cytokine levels.[12]

**The mortality rate in severe sepsis remains just under 30%**

## Corticosteroids improve hemodynamic function

Numerous lines of evidence also indicate that corticosteroids protect vascular tone in sepsis.

Corticosteroids inhibit inducible nitric oxide synthase, a vasodilatory molecule.[13] They also inhibit serum phospholipase $A_2$, leading to decreased production of the vasodilatory compounds prostaglandin $E_1$ and prostacyclin.[14]

Corticosteroids also improve the vascular response to exogenous catecholamines in the septic state. The mechanism may be by preserving adrenergic receptors.[15]

In an elegant experiment, Hinshaw et al[16] induced septic shock in adrenalectomized dogs by giving them infusions of *Escherichia coli*. The dogs had an impaired response to catecholamines that was reversed by glucocorticoid treatment.

Annane et al[17] demonstrated that patients in septic shock who had normal adrenal reserve responded better to vasopressors than did patients with relative adrenal insufficiency.

## Patients with septic shock may have relative adrenal insufficiency and glucocorticoid resistance

Relative adrenal insufficiency and glucocorticoid resistance may arise during severe sepsis. TNF-alpha and IL-6 decrease cortisol production from the adrenal gland and adrenocorticotropic hormone (ACTH) production from the pituitary gland.[18,19] Marik et al[20] found that critically ill patients have inappropriately low levels of ACTH (< 40 pg/mL).

Many investigators have observed an impaired adrenal response in sepsis. Rothwell et al[21] found absolute adrenal insufficiency in only one (3%) of 32 patients with septic shock, but found relative adrenal insufficiency (an increase of < 250 nmol/L in cortisol following ACTH stimulation) in 13 (40%). Annane et al[22] observed relative adrenal insufficiency (defined as an increase in serum cortisol of less than 9 μg/dL 60 minutes after receiving ACTH 250 μg) in 54% of 189 patients with septic shock.

Furthermore, endotoxin infusion and inflammatory cytokines decrease the affinity of glucocorticoids for their receptor ligands, illustrating a possible mechanism of glucocorticoid resistance in sepsis.[23]

## Positive results in animal trials

Glucocorticoids were beneficial in numerous

experiments in animals with sepsis.

Brigham et al[24] demonstrated decreased lung permeability in a sheep model of endotoxemia.

Hinshaw et al[25] induced sepsis in baboons by infusing *E coli*. Five of eight animals who received methylprednisolone and gentamicin 3 hours after the onset of hypotension survived, compared with none of eight animals in a control group.

In a rat model of endotoxemia, dexamethasone ameliorated circulatory failure and renal dysfunction. Furthermore, the dexamethasone-treated rats demonstrated less production of inducible nitric oxide synthase and less infiltration of neutrophils in their kidneys.[26]

In a rat model of sepsis in which the cecum was ligated and perforated, a bolus of methylprednisolone increased survival as much as antibiotics did.[27]

### Results of trials of glucocorticoids in humans with sepsis

Clinical trials of corticosteroids date back to 1963, when the Cooperative Study Group[28] performed a study in patients with severe infection, most of whom had meningitis. Treatment was not beneficial.

Schumer[29] generated a great deal of excitement about corticosteroid therapy for sepsis in 1976, when he published the results of an 8-year, three-armed study comparing high-dose dexamethasone (3 mg/kg by intravenous bolus, repeated in 4 hours if necessary), methylprednisolone (30 mg/kg by intravenous bolus and repeated at 4 hours if necessary), and saline infusion in 172 patients with septic shock. The mortality rate was 10.4% in the steroid groups (11.6% with methylprednisolone and 9.3% with dexamethasone) compared with 38.4% in the placebo group.

Schumer simultaneously published a retrospective review of 328 patients, in whom the mortality rate was 42.5% with saline infusion compared with 14% with steroid treatment. This study was criticized for a number of reasons, including that it did not define adequate antibiotic treatment and supportive management, and it had the potential for selection bias.[30]

Not until 1987 were two large, randomized, placebo-controlled trials of short-course, high-dose corticosteroids reported.

Bone et al[31] gave patients with severe sepsis or septic shock either methylprednisolone 30 mg/kg or placebo for up to four doses within 2 hours of the diagnosis. Similarly, the VA Systemic Sepsis Cooperative Study Group[32] used a methylprednisolone 30 mg/kg bolus followed by a 5 mg/kg infusion for 9 hours vs placebo.[32] Neither study demonstrated a lower mortality rate in the glucocorticoid group; in fact, a trend towards harm was seen in the trial of Bone et al[31] in patients with impaired renal function at baseline.

A Cochrane database meta-analysis of six trials of short-course, high-dose corticosteroids did not show any reduction in all-cause mortality at 28 days (relative risk [RR] 0.97, 95% confidence interval [CI] 0.72–1.31, $P = .84$).[33]

Starting in 1997, investigators began to use lower doses of corticosteroids, giving them for longer courses.[34–38]

Minneci and colleagues[39] at the National Institutes of Health (NIH) performed a meta-analysis and found that trials done after 1997 used a median total hydrocortisone dose of 1,209 mg, vs 23,975 mg in earlier trials. The median duration of therapy after 1997 was 6 days, vs 1 day in the earlier trials. The later trials also used a steroid taper and had a greater percentage of patients in septic shock compared with earlier trials.

**Organ failure in severe sepsis is driven by a systemic inflammatory response**

Another meta-analysis of these trials demonstrated a statistically significant reduction in mortality (RR 0.80, 95% CI 0.67–0.95, $P = .01$) and an increase in shock reversal at 28 days (RR 1.26, 95% CI 1.04–1.52, $P = .02$) with long-course, low-dose corticosteroid therapy.[33]

It must be noted that the dosages used in these trials, while lower than those used in earlier trials, were still supraphysiologic.

Annane et al[37] performed a placebo-controlled, blinded, multicenter trial of low-dose, long-course corticosteroid therapy for septic shock, the largest such trial to date. Three hundred patients were enrolled within 8 hours of the onset of septic shock and were randomized to receive either hydrocortisone 50 mg intravenously every 6 hours along with fludrocortisone 50 μg orally once a day or placebo,

for 7 days. All patients had an ACTH stimulation test at baseline. The primary end point was all-cause mortality at 28 days in the "nonresponder" population, defined as those with a rise in their serum cortisol level of less than 9 μg/dL 1 hour after receiving ACTH 250 μg. Survival time was significantly longer with treatment in both the nonresponders ($P = .02$) and the overall population ($P = .03$), but not in the "responder" population ($P = .71$).

This trial provides the greatest argument in favor of low-dose, long-course glucocorticoid therapy for septic shock.

### Safety of glucocorticoid therapy in severe sepsis

A number of safety concerns accompany the use of corticosteroids in patients with severe sepsis. Potential side effects include worsening of the infection that initiated the sepsis and the development of superinfections, hypernatremia, hyperglycemia, and gastrointestinal bleeding.

In the trial of high-dose methylprednisolone performed by Bone et al,[31] the mortality rate directly attributed to secondary infections was 35% in the treated group vs 7% in the placebo group ($P < .015$).

**Six trials of short-course, high-dose corticosteroids did not show any reduction in mortality**

In the VA Systemic Sepsis Cooperative Study Group trial,[32] secondary infections resolved in 12 of 23 patients in the placebo group compared with 3 of 16 in the treatment group ($P = .03$), although the mortality rates were similar (36% vs 31%).

Cronin and colleagues,[40] in a meta-analysis of nine trials using higher doses of corticosteroids, found a trend towards increased mortality due to secondary infections (RR 1.70, 95% CI 0.70–4.12).

Lefering et al,[41] on the other hand, did not find an increased rate of secondary infections with corticosteroid treatment in another meta-analysis.

The best data on the safety of glucocorticoids in sepsis and septic shock come from a meta-analysis performed by Annane and colleagues of all trials of low-dose and high-dose corticosteroids performed to date.[33] Data from 1,705 patients in 12 trials did not show an increased risk of superinfection in the corticosteroid-treated group (RR 0.93, 95% CI 0.73–1.18, $P = .54$). Data from 1,321 patients in 10 trials did not show a higher rate of gastrointestinal bleeding in the corticosteroid group (RR 1.16, 95% CI 0.82–1.65, $P = .40$). And data from 608 patients in 6 trials did not show an increased risk of hyperglycemia in the corticosteroid-treated group. Data are not available from these trials regarding the relative risk of hypernatremia or hypokalemia in corticosteroid-treated patients.

These data indicate that low-dose, long-course corticosteroids appear to be safe for patients with septic shock.

## CONTROVERSIAL ISSUES

### Which corticosteroid, what dosage?

Mortality data from the clinical trials support the use of no more than 300 mg of hydrocortisone per day in patients with septic shock. In the NIH meta-analysis, there was an inverse linear relationship between steroid dose and survival: the higher the dose the lower the survival rate. Hydrocortisone, given in bolus doses of 50 mg every 6 hours or 100 mg every 8 hours, has been the predominant glucocorticoid strategy in the positive trials, including Annane's trial.[37] Continuous infusions of hydrocortisone were given with benefit in one trial,[35] but head-to-head data are not available to compare these strategies.

Only the trial performed by Yildiz et al[38] used a glucocorticoid other than hydrocortisone, making it impossible to make statements on comparative efficacy of different types of steroids. The trial of Annane et al[37] is the only one that also included daily dosing of a mineralocorticoid, fludrocortisone 50 μg per day. The contribution of the mineralocorticoid to the benefit observed in this trial is unknown.

Given that hydrocortisone has mineralocorticoid activity, that absolute adrenal insufficiency is rare in sepsis, and that using hydrocortisone by itself has been found to be beneficial, the current guidelines for the treatment of septic shock do not advocate the use of fludrocortisone.[42]

### How long to treat?

Although the ideal duration of corticosteroid therapy in septic shock is not known, the five trials since 1997 that demonstrated benefit in septic shock provide some guidance. The

median duration of therapy in these trials was 6 days. Annane et al,[37] in the largest of these trials, used hydrocortisone and fludrocortisone for 7 days.

In three of the five trials, a taper was used either after the discontinuation of pressors or after a period of 3 to 5 days.[39] The concept of a steroid taper is supported by the observation of rebound hypotension and increase in inflammatory markers after abrupt steroid cessation.[43]

### Who should get steroids?

The appropriate target population for corticosteroid therapy in the critically ill is a controversial topic. Results from clinical trials are clear that patients with severe sepsis without hypotension should not receive corticosteroids. In patients with septic shock, issues revolve around the timing of the use of low-dose corticosteroids.

In the largest trial, by Annane et al,[37] therapy was given within 8 hours of the onset of septic shock. A meta-analysis of five recent trials of low-dose hydrocortisone showed that therapy was given at a median time of 23 hours following the development of shock.[39] These data suggest that one can give corticosteroids in situations in which the patient has not improved with early appropriate antibiotic therapy, source control of infection, and early aggressive fluid resuscitation.

Also controversial is whether to base the decision to give corticosteroids on the results of an ACTH stimulation test. The Annane trial saw a benefit in prolonged time to death only in nonresponders.[37]

Minneci et al[39] performed a meta-analysis of the three clinical trials in which results were stratified by response to the ACTH stimulation test. Seventy-five percent of the patients in the meta-analysis are from the Annane trial. Three of these trials reported mortality data, and two of these trials reported shock reversal separately for responders and nonresponders. The effects of treatment on mortality or shock reversal did not statistically differ significantly in the patients with a response to ACTH (6–9 μg/dL) compared with the nonresponders ($P < .2$).

Furthermore, there is no consensus on what baseline level or stimulated level of cortisol in response to ACTH stimulation defines "relative adrenal insufficiency" in critical illness.[42] Hamrahian and colleagues[44] found high-normal or elevated free cortisol levels at baseline and after ACTH stimulation in 66 critically ill patients, many of whom, on the basis of hypoalbuminemia, appeared adrenally insufficient when only serum total cortisol was measured. These data cast doubt on the true incidence and definition of adrenal insufficiency in this population.

In my opinion, the available efficacy and safety data suggest that it is reasonable to give low-dose, long-course corticosteroid therapy to all patients with vasopressor-dependent septic shock irrespective of the results of the ACTH stimulation test.

## THE CORTICUS TRIAL

A large clinical trial called Corticosteroid Therapy of Septic Shock (CORTICUS) is nearing completion, and, hopefully, will answer many of the remaining questions surrounding the use of glucocorticoids in septic shock.

This double-blinded, randomized, placebo-controlled, multicenter European trial is comparing hydrocortisone (50 mg intravenously every 6 hours for 5 days followed by tapering to 50 mg every 12 hours for 3 days and then 50 mg once daily for the last 3 days) with placebo in patients with septic shock. A total of 800 patients will be enrolled. The primary analysis will compare 28-day all-cause mortality in the two treatment groups in patients with less than a 9-μg/dL increase in cortisol level in response to ACTH stimulation.

**Low-dose long-course corticosteroids appear to be safe and effective in septic shock to decrease mortality**

The trial is large enough to examine differential effects in treatment arms in the nonresponders and responders to ACTH stimulation. Also central to the design of the study is an analysis of different definitions of relative adrenal insufficiency, including an examination of free cortisol levels.[42,45]

## CONCLUSIONS

Pending the results of the CORTICUS trial, the current use of corticosteroids in sepsis syndrome is somewhat ambiguous. However, I

can offer the following recommendations:

- There are no data to support the use of corticosteroids in septic patients who are hemodynamically stable, ie, without shock.
- Short courses of high-dose steroids (eg, hydrocortisone > 300 mg/day) should not be used for septic shock. Low-dose hydrocortisone should be given intravenously either as 50 mg every 6 hours for at least 7 days or as a continuous infusion of 10 mg/hour following a loading dose of 50 to 100 mg over 20 to 30 minutes.
- Results of an ACTH stimulation test may not be necessary to determine who should receive glucocorticoid therapy.
- Hydrocortisone should be tapered over at least a few days to prevent rebound hypotension.

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