

# Do Corticosteroids Decrease Mortality in Sepsis?

## EBEM Commentator

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0196-0644/\$-see front matter

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doi:10.1016/j.annemergmed.2004.12.002

[Ann Emerg Med. 2005;45:330-332.]

## SYSTEMATIC REVIEW SOURCE

This is a systematic review abstract, a regular feature of the *Annals'* Evidence-Based Emergency Medicine (EBEM) series. Each features an abstract of a systematic review from the Cochrane Database of Systematic Reviews and a commentary by an emergency physician knowledgeable in the subject area.

The source for this systematic review abstract is: Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y. Corticosteroids for treating severe sepsis and septic shock (Cochrane Review). In: *The Cochrane Library*. Issue 2. Chichester, United Kingdom: John Wiley & Sons, Ltd.; 2004.

The *Annals'* EBEM editors prepared the abstract of this Cochrane systematic review as well as the Evidence-Based Medicine Teaching Points.

## OBJECTIVE

To examine the effects of intravenous corticosteroids on death at 1 month in patients with severe sepsis and septic shock.

## DATA SOURCES

The authors searched the Cochrane Infectious Diseases Group's trial register (August 2003), the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, Issue 3, 2003), MEDLINE (August 2003), EMBASE (August 2003), LILACS (August 2003), reference lists of articles, and contacted trial authors.

## STUDY SELECTION

Randomized and quasirandomized controlled trials of corticosteroids versus placebo or supportive treatment (with antibiotics, fluid replacement, inotropes or vasopressors, mechanical ventilation, and renal replacement therapy) in severe sepsis and septic shock.

## DATA EXTRACTION

Two pairs of reviewers agreed on the eligibility of trials. One reviewer extracted data, which was checked by the other reviewers and the primary author of the article whenever possible. Some missing data were obtained from the trial authors. The methodologic quality of the trials was also

assessed. Relative risks (RR) with 95% confidence intervals (CIs) were reported using a random-effects model.

## MAIN RESULTS

Corticosteroids did not change 28-day all-cause mortality (15 trials, n=2,022, RR 0.92, 95% CI 0.75 to 1.14; random-effects model) and hospital mortality (13 trials, n=1,418, RR 0.89, 95% CI 0.71 to 1.11; random-effects model); however, there was statistically significant heterogeneity, with some evidence that this was related to the dosing strategy. Subgroup analysis on the 5 trials that have tested long courses ( $\geq 5$  days) of low-dose corticosteroids ( $\leq 300$  mg hydrocortisone per day or equivalent of cortisone, methylprednisolone, betamethasone, or dexamethasone) showed a RR for death at 28 days of 0.80 (95% CI 0.67 to 0.95;  $P=.01$ ) in favor of the corticosteroid group. In this subset (4 trials, n=425), corticosteroids reduced ICU mortality (RR 0.83; 95% CI 0.70 to 0.97) and demonstrated less shock by 7 days (RR 1.22; 95% CI 1.06 to 1.40) and 28 days (RR 1.26; 95% CI 1.04 to 1.52). This improvement was not associated with increased gastroduodenal bleeding (10 trials, n=1,321; RR 1.16, 95% CI 0.82 to 1.65), superinfection (12 trials, n=1,705; RR 0.93, 95% CI 0.73 to 1.18), or hyperglycemia (6 trials, n=608; RR 1.22, 95% CI 0.84 to 1.78).

## CONCLUSION

Overall, corticosteroids did not change 28-day mortality and hospital mortality in severe sepsis and septic shock. The subgroup treated with long courses of low-dose corticosteroids, however, had lower 28-day all-cause mortality, ICU mortality, and hospital mortality.

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## COMMENTARY: CLINICAL IMPLICATION

Sepsis is an important health care and emergency department (ED) problem. Each year, severe sepsis occurs in about 3 people per 1,000 population and accounts for 10% of stays in ICUs. The ED approach to sepsis includes early recognition and comprehensive investigation, as well as treatment that includes

the use of intravenous fluid resuscitation, inotropes or vasopressor agents, antibiotics, ventilatory support, and perhaps activated protein C.<sup>1</sup> The central role of the ED in the overall approach to sepsis has been highlighted in the proposed approach to care referred to as early goal-directed therapy.<sup>2</sup> Despite these approaches, overall hospital mortality can be as high as 30% for severe sepsis and 50% to 60% for septic shock.

One important issue for emergency physicians is whether the addition of corticosteroids improves sepsis outcomes, and this Cochrane Review has addressed this question. Almost all trials of corticosteroids in sepsis in the Cochrane Review and previous meta-analyses<sup>3,4</sup> conducted before 1992 yield a relative risk of dying at day 28 of greater than 1.0, and almost all trials conducted after 1992 yielded a relative risk less than 1.0. In 1992, a more precise definition of sepsis was accepted,<sup>5</sup> and it was recognized that septic shock is often accompanied by adrenal insufficiency. Subsequent trials have used long courses ( $\geq 5$  days) of low-dose corticosteroids ( $\leq 300$  mg of hydrocortisone per day), rather than the higher-dose corticosteroids used previously. To explore this, the authors of this Cochrane Review provide a systematic review of the long duration, low-dose trials conducted since 1998.<sup>6</sup> In this meta-analysis, the trials were more homogeneous, and the relative risk for death was 0.80 at 28 days (5 trials,  $n=465$ ; 95% CI 0.67 to 0.95) and 0.83 at hospital discharge (5 trials,  $n=465$ , 95% CI 0.71 to 0.97). Use of corticosteroids reduced mortality in ICUs (4 trials,  $n=425$ , RR 0.83, 95% CI 0.70 to 0.97) and increased shock reversal at 7 days (4 trials,  $n=425$ ; RR 1.60, 95% CI 1.27 to 2.03) and 28 days (4 trials,  $n=425$ ; RR 1.26, 95% CI 1.04 to 1.52) without increasing gastroduodenal bleeding, superinfection, or hyperglycemia. Another recent meta-analysis by Minecci et al<sup>7</sup> reached similar conclusions. The authors note that the treatment effect of corticosteroids is similar in size to that achieved with activated protein C, without the side effects of increased bleeding, increased cost (US\$8,800 versus US\$50), and risk of harm in low-risk patients.

Although the total number of patients is relatively small and it is unclear whether the results pertain to all comers or just to those with true adrenal insufficiency (about 50% of those in septic shock), there appears to be compelling evidence of benefit from corticosteroid use in septic shock. Further research is needed to delineate which patients with septic shock will derive most benefit; however, in the meantime the potential benefits are significant and the adverse effects associated with this approach are limited. These Cochrane reviewers suggest that until there is further research on optimizing diagnostic testing of adrenal insufficiency in patients with septic shock, corticosteroids should be given only to patients with a random cortisol concentration less than or equal to 414 nmol/L (that is, absolute adrenal insufficiency) or a cortisol response to adrenocorticotropin hormone less than or equal to 248 nmol/L (that is, relative adrenal insufficiency). Minneci et al's<sup>7</sup> interpretation of the trials that studied adrenal function is that there is no difference in mortality between those with or without adrenal insufficiency,<sup>7</sup> a discrepancy that is discussed in detail in an

accompanying editorial in the same issue.<sup>8</sup> The role of adrenal functioning and the decision to continue corticosteroids for a 5-day course are decisions that emergency physicians do not need to make, and hopefully an ongoing trial will further guide therapy. In the meantime, it seems reasonable for emergency physicians to administer the first dose of hydrocortisone (100 mg intravenously, or equivalent) for patients with suspected septic shock while awaiting results of further testing.

## TAKE HOME MESSAGE

Long courses of low-dose corticosteroids reduce mortality in septic shock at 28 days in ICUs and in the hospital. They also improve systemic hemodynamics and reduce the time on vasopressor treatment without significantly altering the risk of gastroduodenal bleeding, superinfections, or hyperglycemia.

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## EVIDENCE-BASED EMERGENCY MEDICINE TEACHING POINT

*Grey literature.* Although little consensus exists regarding the definition of "grey literature," it is a term generally used to describe evidence that is hard to find (eg, published in non-MEDLINE or EMBASE journals), is unpublished (eg, abstracts, pharmaceutical company documents), is often not published in traditional locations (such as peer-reviewed journals), or has limited distribution (eg, US Food and Drug Administration reports, graduate student work). High-quality systematic reviews tend to include searches of the grey literature in an attempt to avoid publication bias. Some authors refuse to include these data because the information is hard to find, it is often incomplete, and they question the quality of the evidence; however, the grey literature doesn't necessarily mean non-peer reviewed. The effect of not including evidence from the grey literature in a systematic review is thought to be an over-estimation of the treatment effect<sup>9</sup>; however, this is not always clear.

*Publication dates:* Available online January 29, 2005.

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The American Board of Emergency Medicine (ABEM) and the American Board of Preventive Medicine (ABPM) will administer the certifying examination in Undersea and Hyperbaric Medicine on November 7, 2005.

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The closure date of the Training plus Practice pathway has been extended. Physicians may submit applications under this pathway until the closure of the application cycle for the 2005 examination.

Application materials will be available for ABEM diplomates on March 1, 2005, and will be accepted with postmark dates through July 1, 2005. ABPM diplomates should contact ABPM for application cycle information.

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