Note: This is a two-article spread with a shared commentary. Please scroll down for the second article.

Review: Low-dose but not high-dose corticosteroids reduced all-cause mortality in severe sepsis and septic shock

Annane D, Bellissant E, Bollaert PE, et al. **Corticosteroids for severe sepsis and septic shock: a systematic review and meta-analysis.** BMJ. 2004;329:480-8. Epub 2004 Aug 2.

QUESTION

In patients with severe sepsis and septic shock, are corticosteroids (CSs) more effective than standard therapy for reducing mortality?

METHODS

Data sources: MEDLINE (1966 to August 2003), EMBASE/Excerpta Medica (1974 to August 2003), LILACS (to August 2003), the Cochrane Infectious Disease Group's trials register (up to 2003), the Cochrane Library (Issue 3, 2003); reference list of relevant trials; and contacting authors.

Study selection and assessment: Studies were selected if they were randomized controlled trials (RCTs) or quasirandomized trials in any language and compared intravenous CSs with standard therapy (antibiotics, fluid replacement, inotropes or vasopressors, mechanical ventilation, and renal replacement therapy) alone or with placebo. Study quality assessments included method of randomization, allocation concealment, and blinding.

Outcomes: All-cause mortality at 28 days. Secondary outcomes were mortality in the intensive care unit (ICU) and in hospital, reversal of shock (stable hemodynamic status ≥ 24 h after being weaned from vasopressors) at 7 and 28 days, and adverse events.

MAIN RESULTS

16 RCTs (n = 2063) met the inclusion criteria. Study quality was adequate for allocation concealment in 13 RCTs (81%) and blinding in 11 RCTs (69%). Using a random-effects model, meta-analysis of 15 RCTs showed that the CS and control groups did not differ for 28-day all-cause mortality (Table). Fewer patients who received long courses (≥ 5 d) of low-dose CSs (≤ 300 mg of hydrocortisone or equivalent) died from any cause than did those who received control (Table). Short courses (< 5 d) of high-dose CSs (> 300 mg) did not differ from control for all-cause mortality (8 RCTs, n = 1115, RR 0.97, CI 0.72 to 1.31). 4 RCTs showed that ICU mortality was reduced in more patients who received long courses of low-dose CSs than in control group patients (Table). 13 RCTs showed that the CS and control groups did not differ for mortality in hospital (Table). Hospital mortality was reduced in 5 trials that used long courses of low-dose CSs (Table). More patients who received CSs had shock reversal than did those who received the control intervention at 7 and 28 days (Table). The groups did not differ for adverse events (P > 0.05).

CONCLUSIONS

In patients with severe sepsis and septic shock, corticosteroids (CSs) were not better than standard therapy for reducing all-cause mortality. CSs did not reduce hospital mortality, but reversed shock at 7 and 28 days. Long courses of low-dose CSs reduced all-cause, intensive care unit, and in-hospital mortality at 28 days.

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Corticosteroids (CSs) vs standard treatment given either alone or with a placebo (control) for sepsis and septic shock*

Outcomes	Number of trials (n)	Weighted event rates		RRR/RBI (95% CI)	NNT (CI)
		CSs	Control		
All-cause mortality at 28 d	15 (2022)	30%	33%	RRR: 8% (–13 to 26)	Not significant
Hospital mortality	13 (1418)	35%	39%	RRR: 11% (–11 to 29)	Not significant
Reversible shock at 7 d	6 (728)	63%	45%	RBI: 42% (2 to 96)	6 (3 to 39)
		Long courses (≥ 5 d) of low-dose (≤ 300 mg) CSs	Control		
All-cause mortality	5 (465)	45%	56%	RRR: 18% (2 to 31)	9 (6 to 40)
ICU mortality	4 (425)	50%	61%	RRR: 16% (1 to 28)	10 (6 to 66)
Hospital mortality	5 (465)	52%	62%	RRR: 14% (0 to 26)	10 (6 to 56)
Reversible shock at 28 d	4 (425)	56%	43%	RBI: 22% (3 to 45)	8 (5 to 55)

*ICU = intensive care unit. Other abbreviations defined in Glossary; weighted event rates, RRR, RBI, NNT, and CI calculated from data in article using a random-effects model.

COMMENTARY

Both clinicians and researchers have hypothesized 2 distinct mechanisms of CS therapy, which might improve outcomes for patients with severe sepsis. The first premise is that high-dose CSs suppress the deleterious and uncontrolled systemic inflammatory response of severe sepsis. The second theory is that relatively low doses of CSs address the physiologic needs of patients with sepsis-associated adrenal insufficiency.

The 2 reviews by Annane and colleagues and Minneci and colleagues highlight pivotal advances related to CS therapy in sepsis and introduce new clinically important insights. The systematic review by Annane and colleagues confirms earlier findings that high-dose CS therapy in severe sepsis and septic shock does not improve survival and may cause harm as a result of secondary infections. In striking contrast, however, both reviews showed that a 5- to an 11-day course of low-dose CSs (200 to 300 mg of hydrocortisone per d) accelerated shock reversal and improved survival at 28 days, ICU discharge, and hospital discharge in patients with vasopressor-dependent septic shock.

The 17 original studies of these reviews differ extensively. Methodological quality was generally superior in the more recent trials. Among the pool of over 2000 patients, study populations from recent trials were uniformly sicker. Although early studies included an assortment of patients with sepsis, severe sepsis, or septic shock, recent trials focused almost exclusively on patients with vasopressor-dependent septic shock. Control-group mortality rates were correspondingly higher among later trials.

Protocols for CS administration also varied. Early trials used higher daily doses over relatively short periods, while recent trials investigated longer courses of lower doses in the physiologic range. Interestingly, total steroid doses were larger in the earlier trials. Finally, the primary

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Review: Glucocorticoids reduced mortality in sepsis in recent (post-1997) but not previous (pre-1989) trials, or all trials combined

Minneci PC, Deans KJ, Banks SM, Eichacker PQ, Natanson C. **Meta-analysis: the effect of steroids on survival and shock during sepsis depends on the dose.** Ann Intern Med. 2004;141:47-56.

QUESTION

In patients with sepsis, are glucocorticoids more effective than a control intervention for reducing mortality?

METHODS

Data sources: Studies were identified by searching MEDLINE (1988 to April 2003) {and included trials from a previous meta-analysis}*.

Study selection and assessment: Studies were selected if they were randomized controlled trials (RCTs) that enrolled adult patients with sepsis (documented site or strong suspicion of infection, temperature > 38 °C or < 36 °C, heart rate > 90 beats/min, respiratory rate > 20 breaths/min, and leukocyte count > 12×10^9 cells/L) or septic shock (hypotension despite fluid resuscitation plus hypoperfusion abnormalities), had a primary endpoint (either the discontinuation of vasopressor therapy or a change in survival), and compared glucocorticoids with a control intervention (antibiotics, vasopressors, or fluids) with or without placebo. Study quality was assessed on method and adequacy of randomization, blinding, completeness of follow-up, adherence to treatment protocols, and cointerventions.

Outcomes: Survival at 14 to 28 days, and reversal of shock.

MAIN RESULTS

14 RCTs (n = 1717) met the selection criteria. RCTs were partitioned according to publication date: previous studies (9 RCTs published before 1989) and recent studies (5 placebo-controlled RCTs published after 1997). 4 of the 5 recent RCTs had complete follow-up and adequate randomization and enrolled patients with vasopressor-dependent septic shock. Previous RCTs used a wider range of inclusion criteria (from "severe infections" to shock). Glucocorticoids used were hydrocortisone, betamethasone, dexamethasone, methylprednisolone, and prednisolone. Recent RCTs administered glucocorticoids later (23 h vs < 2 h, P = 0.02) and for longer courses (6 vs 1 d, P = 0.01) of lower-dose steroid therapy (1209 mg vs 23 975 mg, P = 0.01) than previous RCTs. Using a fixed-effects model, meta-analysis of 13 RCTs (previous and recent) showed that glucocorticoid and control groups did not differ for survival (Table). The groups did not differ for survival in previous RCTs (Table). Of 4 recent RCTs that reported mortality and reversal of shock, more patients who received glucocorticoids survived (Table) and had reversal of shock (3 RCTs [relative benefit range 1.13 to 3.24, 95% CI 0.86 to 7.01]; 1 RCT [hazard ratio 1.54, CI 1.10 to 2.16]) than did those who received the control intervention.

CONCLUSIONS

In patients with sepsis, glucocorticoids reduced mortality more than a control intervention in trials published after 1997, but not in trials published before 1989 or in all trials combined.

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*__Cronin L, Cook DJ, Carlet J, et al.__ Crit Care Med. 1995;23:1430-9.

Glucocorticoids (GCs) vs control (antibiotics, vasopressors, or fluids) with or without a placebo for reducing mortality in sepsis and septic shock at 14 to 28 days†

Trials	Number of trials (n)	Weighted event rates		RRR/RRI (95% CI)	NNT/NNH (CI)
		Control	GCs		
All trials	13 (1717)	39%	40%	RRR: 1% (–10 to 12)	NNT: Not significant
Previous trials	9 (1297)	36%	35%	RRI: 7% (–7 to 23)	NNH: Not significant
Recent trials	4 (420)	47%	57%	RRR: 17% (1 to 31)	NNT: 11 (6 to 134)

†Previous trials = published before 1989; recent trials = published after 1997. Abbreviations defined in Glossary; weighted event rates, RRR, RRI, NNT, NNH, and CI calculated from data in article using a fixed-effects model.

COMMENTARY *(continued from page 30)*

studies measured adverse effects of CS therapy (secondary infection, gastrointestinal bleeding, organ system failure, and hyperglycemia) inconsistently, although each of the systematic reviews provided a comprehensive and quantitative summary.

Despite careful explorations to understand the divergent results between early and recent trials, the only compelling explanation relates to differences in daily dose and duration of therapy. Disparities in quality did not appear to influence study findings but cannot be ruled out. Similarly, the relation between sepsis severity and therapeutic benefit is uncertain. For now, the evidence is clear only for those patients with septic shock, for whom low-dose therapy confers a statistically significant and clinically important survival benefit.

An unresolved issue is the role for adrenal testing to select patients for a course of CS therapy. On this issue, the authors of the 2 reviews disagree. 3 relatively recent trials conducted subgroup analyses in patients with and without biochemical evidence of adrenal insufficiency. Observed differences between the subgroups were relatively small, not statistically significant, and inconsistent across the 3 trials (as shown in the review by Minneci and colleagues). Taking the limitations of subgroup analyses and the prevailing uncertainty about adrenal testing in critically ill patients into consideration, findings of these subgroup analyses do not support withholding CS therapy while waiting for results of adrenal function tests. A widely accepted alternative approach is to test and treat all patients with vasopressor-dependent septic shock (barring contraindications), and to consider weaning from steroids those whose test results (when available) rule out a diagnosis of adrenal insufficiency.

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