Hydrocortisone and fludrocortisone improved 28-day survival in septic shock and adrenal insufficiency

Annane D, Sébille V, Charpentier C, et al. **Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock.** JAMA. 2002;288:862-71.

QUESTION

In patients with septic shock and relative adrenal insufficiency, is replacement therapy with hydrocortisone and fludrocortisone more effective than placebo for improving 28-day survival?

DESIGN

Randomized (allocation concealed*), blinded (clinicians, patients, and pharmacists),* placebo-controlled trial with 1-year follow-up.

SETTING

19 intensive care units in France.

PATIENTS

299 adult patients (mean age 61 y, 50% women) with septic shock. Exclusion criteria included acute myocardial infarction, pulmonary embolism, advanced cancer, AIDS, and contraindication or formal indication for corticosteroids. Follow-up was 100%.

INTERVENTION

All patients received the short corticotropin test (250 μg of tetracosactrin intravenously) for diagnosis of relative adrenal insufficiency (RAI), defined as an increase in cortisol level of ≤ 248.31 nmol/L (9 μg/dL). Subsequently, patients were allocated to treatment with corticosteroids (n = 150 [including in retrospect 114 with RAI]) or placebo (n = 149 [including in retrospect 115 with RAI]). The corticosteroids were a combination of hydrocortisone (50-mg intravenous bolus every 6 h) and fludrocortisone (50-μg tablet/d) for 7 days.

MAIN OUTCOME MEASURES

The primary outcome was the survival distribution (time to and rate of all-cause mortality) from randomization to 28 days of follow-up in patients with RAI.

MAIN RESULTS

Analysis was by intention to treat. At 28 days, median time to death was greater in the corticosteroid group than in the placebo group (24 vs 12 d, P = 0.02) for patients with RAI. The corresponding rate of all-cause mortality was lower in the corticosteroid group than in the placebo group (Table). For all randomized patients, the groups did not differ for all-cause mortality (55% vs 61%, P = 0.09).

CONCLUSION

In patients with septic shock and relative adrenal insufficiency, replacement therapy with hydrocortisone and fludrocortisone was effective for improving 28-day survival.

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For correspondence: Dr. D. Annane, Hôpital Raymond Poincaré, Garches, France. E-mail djillali.annane@rpc.ap-hop-paris.fr. ∎

*See Glossary.

Hydrocortisone plus fludrocortisone (steroids) vs placebo in septic shock and relative adrenal insufficiency at 28 days†

Outcome	Steroids	Placebo	Hazard ratio (95% CI)	NNT (CI)
All-cause mortality	53%	63%	0.67 (0.47 to 0.95)	7 (4 to 49)

†NNT and CI defined in Glossary.

COMMENTARY

The study by Annane and colleagues assessed the effectiveness of low doses of corticosteroids in patients with septic shock and concluded that treatment reduced the mortality rates in patients with evidence of RAI. Although these results are exciting, several issues must be considered.

First, compared with many recent clinical sepsis trials (1), the mortality rate in this study was unusually high (i.e., 61% in the overall control group). This may be because the criteria used to define septic shock for enrollment, which included the need for mechanical ventilation, differed from those of the American College of Chest Physicians–Society of Critical Care Medicine Consensus Conference frequently used in other trials (2). Nevertheless, increasing evidence exists that antiinflammatory agents are beneficial in septic patients with severe infection and a high risk for death, but they may be ineffective or even harmful if the mortality risk is low (1).

Second, the survival rate with treatment in the corticotropin-responder group in this study was 8% less than that in controls. This difference was not statistically significant, but responders represented a relatively small subset of the total group of septic patients studied. It is of concern that this divergence could become statistically significant if a larger number of patients were included in this group. If significant, then accurate assessment of adrenal responsiveness would be critical before institution of steroid treatment.

Third, the 3-level prognostic classification system, originally proposed by this group and often applied clinically, was not used in this study (3). As a result, it is unclear whether the diagnosis of RAI in sepsis based on basal cortisol levels alone could predict responsiveness to low-dose corticosteroids.

This study provides important insights on the potential application of corticosteroids in sepsis, but the findings are not definitive. A prospective study with stratification for severity of illness, baseline cortisol, and corticotropin-stimulation testing is needed to further assess the usefulness of low-dose corticosteroid treatment.

John Beigel, MD
Peter Eichacker, MD
National Institutes of Health
Bethesda, Maryland, USA

References

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3. **Annane D, Sébille V, Troché G, et al.** A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. JAMA. 2000;283:1038-45.