Best evidence in critical care medicine

Treatment: adrenal replacement therapy improves survival in patients with septic shock

Article appraised

Annane D, Sebille 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.

Structured abstract

Question: In patients with septic shock and relative adrenal insufficiency, does adrenal replacement therapy improve survival compared to placebo?

Design: Blinded (patients, investigators, and outcome assessors), randomized placebo-controlled trial.

Setting: Nineteen intensive care units across France between September 1995 and March 1999.

Patients: Three hundred thirty men and women > 18 yr of age, who met standard criteria for septic shock. There were no differences in baseline characteristics.

Intervention: After undergoing a 250 μg synthetic adrenocorticotropin (ACTH) stimulation test, patients were allocated to receive hydrocortisone 50 mg *iv* Q6H and fludrocortisone 50 μg tablet once daily or matching placebos for seven days.

Main outcome measures: The primary outcome was 28-day survival in patients with sepsis and relative adrenal insufficiency (designated as nonresponders to the corticotropin test on the basis of less than a 248 $nmol \cdot L^{-1}$ incremental change in cortisol following a 250 μg ACTH stimulation test). Secondary outcomes included time to withdrawal of vasopressor therapy.

All patients were evaluated on an intention-to-treat basis (one patient was excluded due to consent withdrawal; one patient who died prior to placebo administration was included).

Results: Seventy-six percent (229 of the 330 patients) were nonresponders to the ACTH stimulation test (115 in the placebo group; 114 in the treatment group).

For the primary outcome, mortality in the nonresponder treatment group was 53% (60 out of 114) *vs* 63% (73 out of 115) amongst the nonresponder placebo group [hazard ratio 0.67; 95% confidence interval (CI) 0.47 – 0.95; $P = 0.02$].

For the secondary outcome, vasopressor therapy was withdrawn more often within 28 days in the nonresponder treatment group *vs* the nonresponder placebo group (57% *vs* 40% of patients; hazard ratio, 1.91; 95% CI, 1.29 – 2.84; $P = 0.001$).

Amongst responders, there were no significant differences between treatment and placebo groups. Adverse event rates were similar in groups of responders and nonresponders.

Conclusion: Adrenal replacement therapy in patients with relative adrenal insufficiency and sepsis improves 28-day survival without increasing adverse events.

Author's recommendation: After performing a 250 μg ACTH stimulation test, adrenal replacement therapy should be instituted in all patients with sepsis requiring inotropic support until results are made available.

Funding: Groupe d'Étude et de Recherche sur le Médicament (GERMED).

Commentary by H. Meggison and G. Jones

This study has demonstrated that a poor incremental change in cortisol in response to adrenocorticotropin (ACTH) is a strong, consistent, and independent predictor of mortality in patients with septic shock. As septic shock is associated with multiple organ failure, it is biologically plausible that endocrine organs are no exception. This study has changed clinical practice in demonstrating that adrenal replacement therapy offers a clear benefit on mortality that seems to be generalizable to all patients with vasopressor dependent septic shock. The question is *should* these findings be generalized to all patients?

First, it is important to consider the complexity of the hypothalamic-pituitary-adrenal axis.
Adrenocorticotropin is not the sole stimulus for cortisol secretion. The inflammatory mediators in sepsis cause positive and negative feedback directly on the adrenal glands as well as the hypothalamus and pituitary.[1] While the beneficial effects of cortisol on blood vessel and immune responsiveness is crucial, interfer-

ing with the complex balance of the neuro-endocrine-immune system by providing exogenous corticosteroids is not without risk. Further, the adverse metabolic effects such as hyperglycemia are to be considered. While responders who received treatment in the trial did not experience any benefit, and appeared to have no adverse outcomes, this study was not powered to demonstrate the opposite hypothesis (a deleterious effect of corticosteroids).

Second, uncertainty exists as to the mechanisms underlying relative adrenal insufficiency. There is emerging evidence for hypothalamic, pituitary and adrenal dysfunction related to sepsis, as well as tissue resistance to stress hormones.[2] This may explain why both high and low levels of total cortisol in sepsis have been associated with mortality.[3] While the 250 μg ACTH stimulation test was used in this study, it would be interesting to know if patients would respond similarly to the low-dose (1 μg) test. Perhaps some patients were able to overcome ACTH resistance with the high-dose test.

Third, approximately 10% of cortisol is unbound (bioavailable) in the non-stressed state, and up to 90% becomes unbound in inflammatory illness.[4] The precise amount of bioavailable cortisol, however, may vary in relation to changes in binding proteins and receptor sensitivity.[4] In considering the interpretation of cortisol measurements, cortisol levels are unlikely to fully reflect cortisol activity in severe sepsis.

Finally, 133 of the 229 (45%) patients in the non-responder group met criteria for absolute adrenal insufficiency with stimulated cortisol levels of < 550 $nmol \cdot L^{-1}$.[5] Sixty-nine of the non-responders (30%) who were included in the final analysis had received etomidate, an anesthetic agent known to cause adrenal insufficiency.[6] This raises an important ethical issue as some of these patients received placebo. Their inclusion in the non-responder placebo group may have contributed heavily to the higher mortality. Regardless, at least some patients who did not receive etomidate met criteria for absolute adrenal insufficiency. It would be of interest to know if these patients had similarities and whether adrenal pathology was identified at autopsy.

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