



## Evidence-Based Medicine Journal Club

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### Journal club critique

## The low-dose ACTH test in the ICU: Not ready for prime time

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### Expanded Abstract

#### Citation

Siriaux V, De Backer D, Yalavatti G, Melot C, Gervy C, Mockel J, Vincent JL: Relative adrenal insufficiency in patients with septic shock: comparison of low-dose and conventional corticotropin tests. *Crit Care Med* 2005, 33:2479-2486 [1].

#### Objective

To compare a low-dose (1 µg) adrenocorticotrophic hormone (ACTH) stimulation test with the more standard (250 µg) test for the diagnosis of relative adrenal insufficiency.

#### Methods

**Design and setting:** Diagnostic study in a thirty-one bed mixed medico-surgical department of intensive care

**Patients:** Forty-six consecutive patients with septic shock.

**Intervention:** Corticotropin stimulation tests (low-dose test, 1 µg, and standard 250-µg test), performed consecutively at an interval >4 hrs.

**Measurements and main results:** In each test, serum cortisol levels were measured before (T0) and 30 (T30), 60 (T60), and 90 (T90) mins after corticotropin injection. The maximal increase in cortisol ( $\Delta_{max}$ ) was calculated as the difference between T0 and the highest cortisol value at T30, T60, or T90 and considered as adequate if >9 µg/dL (250 nmol/L). Nonresponders to the low dose test had a lower survival rate than responders to both tests (27 vs. 47%,  $p = .06$ ; Kaplan Meier curves). Interestingly, nonresponders to high-dose test received hydrocortisone treatment and had a similar survival to responders. Multivariable logistic regression disclosed that the response to the combined low-dose test and high-dose test was an independent predictor of survival (odds ratio 28.91, 95% confidence interval 1.81–462.70,  $p = .017$ ), whereas basal or maximal cortisol levels in both tests were not.

### Conclusion

The low-dose test identified a subgroup of patients in septic shock with inadequate adrenal reserve who had a worse outcome and would have been missed by the high-dose test. These patients may also benefit from glucocorticoid replacement therapy.

### Commentary

A variety of methods have been used to detect adrenal insufficiency in patients with septic shock, including the 250 µg ACTH stimulation test (standard or “high-dose” test), the 1 µg ACTH stimulation test (“low-dose” test), measurement of random cortisol levels, measurement of free cortisol levels, and determination of the hemodynamic response to hydrocortisone. However, only the high-dose ACTH test was shown to detect patients who are likely to receive a mortality benefit from corticosteroid (steroid) replacement therapy [2]. Based on these findings, corticosteroid replacement has become the standard of care for septic shock patients who fail to demonstrate an increase in plasma cortisol level by 9 µg/dL or more after injection of 250 µg of ACTH. Recently, a subgroup of septic shock patients was identified that responded adequately to the high-dose ACTH test, yet inadequately to the low-dose test [3]. The impact of this finding on outcome is unclear, since all patients in the study received replacement doses of corticosteroids.

In the current study, Siriaux and colleagues found that as many as 50% of high-dose responders failed to respond to the low-dose test and that this discordant subset of patients showed a trend toward worse 28-day mortality. The authors speculated that the low-dose test might identify an additional group of septic shock patients who can benefit from therapy with corticosteroids.

Strengths of this study include the use of standard definitions for septic shock and infection as well as invasive monitoring with goal directed therapy. Patients were excluded if they received steroids in the month prior or if they were given etomidate <24 hours before the ACTH test. This latter exclusion was critical, since etomidate seems to cause significant but transient adrenocortical suppression especially during the first 24 hours after administration [4], though the duration of adrenal suppression induced by etomidate is controversial [5]. Exclusion of these patients may explain the lower prevalence of relative adrenal insufficiency in this study as compared to others [2,6], although other factors, such differences in illness severity and the type of cortisol assay used, also may have played a role.

Because the subset of patients with discordant results did not receive replacement steroids, the clinician is left with a bit of a conundrum. On one hand, we may be missing patients with septic shock who can benefit from steroid replacement; on the other hand, steroids can cause important side effects, such as increased risk of infection or impair wound healing. Furthermore, there is no evidence of that administering corticosteroid improves outcome for patients, who fail to respond to the low-dose ACTH test.

### Recommendation

The current evidence showing improved mortality with steroid replacement is limited to patients with septic shock who are nonresponders to the high-dose ACTH test. It remains to be seen whether the subgroup of nonresponders identified by the low-dose test also will benefit from treatment with replacement doses of corticosteroids. Until such data are available, we recommend that only nonresponders to the high-dose test receive replacement steroids.

### Competing interests

The authors declare no competing interests.

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