Commentary

Cortisol replacement for severe sepsis and septic shock: what should I do?

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Abstract

Based on several recently completed randomized controlled trials, cortisol replacement is likely to become a standard of care for vasopressor dependent septic shock. Further studies are needed in order to accomplish whether this treatment should be limited to patients with a blunted cortisol response to corticotrophin. Similarly, in patients with severe sepsis who do not need vasopressors, the benefit/risk ratio of cortisol replacement remains to be assessed.

Keywords ACTH test, hydrocortisone, sepsis, shock, survival

In this issue of *Critical Care,* Yildiz and colleagues reported the first randomized, controlled trial on the efficacy and safety of physiologic doses of steroids in severe sepsis [1]. During the past 5 years, five phase II trials and a phase III placebo-controlled trial on cortisol replacement, i.e. prolonged treatment with physiologic doses of steroids, have been completed in patients with vasopressor-dependent septic shock (Table 1) [2–6]. Two of them have already been published in peer-reviewed journals [2,3], three have been published in abstract form and will be published shortly in peer reviewed journals [4–6], and the results of a phase II trial that has just been completed will be available very soon (Oppert and colleagues, personal communication). These trials have consistently shown beneficial effects of cortisol replacement on the amount of vasopressors [2–6], on the duration of shock [2–4,6], on the duration and intensity of organ dysfunction [3,6], and on the intensity of the systemic inflammatory response [5,6]. The survival benefit observed with cortisol replacement in several phase II trials [2,4] was recently confirmed by the phase III trial [6]. In all these trials, cortisol replacement was never associated with even a trend toward serious side effects. A confirmatory phase III, multinational, placebo-controlled trial (the CORTICUS study) is under way, and results should be available within the next 3 years. In the meantime, given the consistency of the results across available trials, cortisol replacement should be considered as a standard of care for patients with vasopressor-dependent septic shock. Yildiz and colleagues found that, in patients with severe sepsis, irrespective of the need for vasopressors, treatment for 10 days with prednisolone given intravenously twice daily (5 mg at 6 a.m. and 2.5 mg at 6 p.m.) was associated with a 20% absolute reduction in mortality within 28 days [1]. These findings are very challenging, because they suggest that cortisol replacement might be introduced in severe sepsis as well as in vasopressor-dependent septic shock, and that the mechanisms underlying the favorable effects of the treatment might not be limited to a reduction of the need for vasopressors. Obviously, a phase III trial must be set up to confirm the potential survival benefit of cortisol replacement in patients with severe sepsis who are not vasopressor-dependent.

The study by Yildiz and colleagues addressed another important issue, i.e. the need for an adrenocorticotropic hormone (ACTH) test to identify patients with severe sepsis or septic shock who will benefit from cortisol replacement [1]. In this small trial, the effects of steroids were not significantly altered by the results of a short ACTH test. However, there were only 14 nonresponders (5 in the steroid group and 9 in the placebo group) to the test, i.e. a cortisol increment after a 250-μg intravenous bolus of ACTH of less than 9 μg/dl, as previously defined [7,8]. Subsequently, in this subset of patients with occult adrenal insufficiency, the 15.6% absolute reduction in 28-day mortality in favor of the steroid group was not statistically significant. Among the six completed trials of cortisol replacement in septic shock, only two reported separate data according to the results of a

Table 1

Recently completed randomized, controlled trials of cortisol replacement in septic shock

Study	Methods	Participants	Interventions	Outcome	Comments
Bollaert *et al.,* 1998 [2]	Randomized, two-center, double blind, parallel groups	N = 41, adults only Vasopressor-dependent septic shock	Hydrocortisone, 300 mg per day (100 mg i.v. bolus) for 5 days and then either stopped (if no effect on shock reversal) or progressively tapered; or placebo	Shock reversal, death, complications	Improved time to shock reversal in 28-day survival No increase in complication rates
Briegel *et al.,* 1999 [3]	Randomized, monocenter, double blind, parallel groups	N = 40, adults only Vasopressor-dependent septic shock	Hydrocortisone, loading dose of 100 mg in 30 min followed by continuous infusion 0.18 mg/kg per h for 6 days and then progressively tapered in steps of 24 mg/day; or placebo	Shock reversal, organ dysfunction, death	Improved time to shock reversal in organ dysfunction free-days No increase in complication rates
Chawla *et al.,* 1999 [4]	Randomized, monocenter, double blind, parallel groups	N = 41, adults only Vasopressor-dependent septic shock	Hydrocortisone, 300 mg per day (100 mg i.v. bolus) for 5 days and then either stopped (if no effect on shock reversal) or progressively tapered; or placebo	Shock reversal, death, complications	Improved time to shock reversal in 28-day survival No increase in complication rates
Keh *et al.,* 1999 [5]	Randomized, placebo-controlled, monocenter, double blind, crossover	N = 40, adults only Vasopressor-dependent septic shock	Hydrocortisone, loading dose of 100 mg in 30 min followed by continuous infusion 0.18 mg/kg per hour for 3 days; or placebo	Systemic inflammation, systemic and pulmonary hemodynamics, vasopressor requirement, complications	Improvement in systemic inflammation, hemodynamics, and vasopressor requirements No increase in complication rates
Annane, 2000 [6]	Randomized, placebo-controlled, multicenter, double blind, parallel groups	N = 300, adults only Vasopressor-dependent and ventilator-dependent septic shock	Hydrocortisone 200 mg/day (50 mg i.v. bolus) + fludrocortisone 50 μg/day (oral) for 7 days or their respective placebo	28-day survival, shock reversal, organ dysfunction reversal, complications	Improvement in shock reversal and mortality No increase in complication rates

short corticotropin test [2,6], and only one trial was adequately powered to assess the survival benefit of cortisol replacement in patients with occult adrenal insufficiency [6]. In fact, in this trial, cortisol replacement dramatically improved rates of survival for 28 days in the intensive care unit or elsewhere in the hospital in the nonresponders to the ACTH test but not in those having an increase in cortisol levels of more than 9 μg/dl after ACTH. However, this trial was not adequately powered to allow definite conclusions regarding patients deemed to have normal cortisol response to ACTH and we therefore need to wait for the results of the CORTICUS study. In the meantime, cortisol replacement should be considered only in vasopressor-dependent septic shock with occult adrenal insufficiency. As the results of the ACTH test might not be available everywhere at all times, it is recommended that cortisol replacement be started immediately after the ACTH test is performed, and that in the light of the results of the test, treatment could be continued for up to 7 days in nonresponders and stopped in patients with normal cortisol response to ACTH.

Competing interests

None declared.

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