Letter

# Unanswered questions from Corticus and pragmatic suggestions

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See related commentary by Vincent, http://ccforum.com/content/12/2/141

Professor Vincent, in an eloquent commentary in *Critical Care*, calls for a further trial into supraphysiological corticosteroid therapy in vasopressor-resistant shock [1]. Together with editorials in several of the intensive care journals, he has pointed out many of the shortcomings in the Corticus trial [2]. We would like to add to this chorus by posing a further question to the authors and putting forward some suggestions. Regrettably, we are prohibited from addressing these directly due to the Letters policy of the journal in which the original paper was published.

Data from numerous sources suggest that the earlier shock is reversed, the better the outcome – be it mortality, morbidity, length of stay or other surrogate endpoints. In the Corticus study, the median time to shock reversal was 2 to 3 days shorter in the hydrocortisone group (see Table 1). Despite this, no outcome improvement was demonstrated. No investigation, or explanation, of this apparent discrepancy has been forthcoming. Sequential Organ Failure Assessment scores were performed at the time of study enrolment, but no serial Sequential Organ Failure Assessment score data are presented. If available, these data would be intriguing.

Following the publication of the Corticus data, a consensus statement regarding the diagnosis and management of corticosteroid insufficiency in critically ill adult patients has been published [3]. Together with a detailed review by Dickstein and Saiegh [4], this statement suggests a working diagnostic paradigm. However, we would like to suggest the following three pragmatic definitions of functional hypoadrenalism, which future trial designers might with wish to consider and which we currently employ.

First, patients with septic shock requiring high-dose vasopressors – defined as requiring ≥0.2 μg/kg/minute norepinephrine (or equivalent), who are not volume responsive (defined as a ≥10% increase in stroke volume following a 3 ml/kg fluid bolus administered in ≤5 min) and who are hyperdynamic (defined as a cardiac index ≥2.8 l/min/m$^2$).

**Table 1**

**Time to shock reversal data from the Corticus study [2]**

| | Median time to shock reversal (days) | | |
|---|---|---|---|
| | Corticotrophin responders | Corticotrophin nonresponders | All patients |
| Control | 5.8 | 6.0 | 5.8 |
| Hydrocortisone | 2.8 | 3.9 | 3.3 |

Patients with evidence of acute myocardial depression or chronic insufficiency should be considered separately.

Second, patients who, having been stable for ≥2 hours on a dose of vasopressor, develop increasing dose requirements (≥20% increase), are unresponsive to a volume bolus (as above) and are hyperdynamic (as above).

Third, patients whose dose of vasopressor cannot be weaned ≥24 hours following initiation of appropriate broad-spectrum antimicrobial therapy and/or effective source control.

Furthermore, this therapy should be withdrawn from patients who fail to demonstrate a ≥20% decrease in vasopressor requirement to maintain the same mean arterial pressure 60 minutes after the initial dose of hydrocortisone. Due to the pharmacokinetics of hydrocortisone, we favour a 100 mg intravenous bolus followed immediately by initiation of a 10 mg/hour intravenous infusion.

Finally, we would like to promote two recently published papers that offer useful insights into the pharmacodynamics of supraphysiological steroid therapy in vasopressor-resistant shock. Firstly, Druce and colleagues make a convincing argument that the principal effect of hydrocortisone is as a mineralocorticoid and not as an anti-inflammatory [5].

Secondly, Kaufman and colleagues [6] found that hydrocortisone administered as described above does have some arguably clinically valuable anti-inflammatory effects but, in addition, enhances neutrophil phagocytosis. This has led us to conclude that, in the absence of a systemic form of fludrocortisone and with the unreliable enteral absorption of drugs, systemic hydrocortisone monotherapy at optimal mineralocorticoid doses should be the therapy of choice.

## Authors' response

Charles L Sprung, Djillali Annane, Didier Keh and Josef Briegel, for the Corticus Study Group

We thank *Critical Care* for the opportunity to respond to the letter of Dr Bauer and colleagues. They question the apparent discrepancy between a shorter time to shock reversal in the hydrocortisone group and no outcome improvement, as did the Corticus investigators. In the Corticus study we noted that 'The duration of the administration of corticosteroids may be pertinent, with the possibility that any gain that was achieved by an earlier reversal of shock was counterbalanced by later complications' [2]. Later we mention the complications – 'an increased incidence of superinfection, including new episodes of sepsis or septic shock, in the hydrocortisone group' [2].

Two recent consensus statements with guidelines have been published after reviewing the Corticus data [3,7], suggesting that intravenous hydrocortisone be given *only* to adult septic shock patients after their blood pressure has been confirmed to be poorly responsive to fluid resuscitation and vasopressor therapy. Although clinicians are frustrated with the lack of explicit recommendations for thresholds for blood pressure, volume resuscitation and vasopressor treatment, the group of experts for both consensus statements – after deliberating with this issue for many months – chose not to give more explicit recommendations because there are simply insufficient data to make such specific recommendations. Experts may provide their own personal opinions and beliefs. Unfortunately, until further quality studies provide answers to the present uncertainties, clinicians will be forced to rely on their expertise in providing the art of medicine and not only the science of medicine.

## Competing interests

The authors declare that they have no competing interests.

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