Glucocorticoids in sepsis: dissecting facts from fiction

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Abstract
An intact hypothalamic-pituitary-adrenal axis with effective intracellular glucocorticoid anti-inflammatory activity is essential for host survival following exposure to an infectious agent. Glucocorticoids play a major role in regulating the activity of nuclear factor-kappa-B, which has a crucial and generalized role in inducing cytokine gene transcription after exposure to an invading pathogen. Severe sepsis is, however, associated with complex, hypothalamic-pituitary-adrenal axis alterations, which may result in decreased production of cortisol as well as glucocorticoid tissue resistance.

Inadequate intracellular glucocorticoid activity, referred to as critical illness-related corticosteroid insufficiency, typically results in an exaggerated proinflammatory response [1]. Patients with severe sepsis or septic shock are therefore frequently treated with exogenous glucocorticoids. While there are large geographic variations in the prescription of glucocorticoids for sepsis, up to 50% of intensive care unit patients receive such therapy [2]. Despite over 30 years of investigation and over 20 meta-analyses, the use of glucocorticoids in patients with sepsis remains extremely controversial and recommendations are conflicting.

The most important recent studies are that of Annane and colleagues [3] and the Corticosteroid Therapy of Septic Shock (CORTICUS) study [4]. Both of these studies have important limitations: 24% patients received etomidate in the study by Annane and colleagues, whereas 19% received etomidate in the CORTICUS study. The benefit of steroids in the study by Annane and colleagues may have been restricted largely to those patients who received etomidate [5]. Furthermore, only patients with ‘refractory septic shock’ were enrolled in the Annane study whereas, as a result of an overwhelming selection bias, only approximately 5% of eligible patients were enrolled in the CORTICUS study [6]. A more recent study found no benefit from a 7-day course of 40 mg of prednisolone in patients hospitalized with community-acquired pneumonia [7].

In the study by Annane and colleagues [3], patients received 50 mg of hydrocortisone intravenously every 6 hours for 7 days, whereas in the CORTICUS study [4], patients received this dose for 5 days, followed by a tapering off over a further 5 days. Recently, two longitudinal studies in patients with severe community-acquired pneumonia found high levels of circulating inflammatory cytokines 3 weeks after clinical resolution of sepsis [8,9]. These data suggest that patients with severe sepsis may have prolonged immune dysregulation (even after clinical recovery) and that a longer course of corticosteroids may be required. The use of a continuous infusion of hydrocortisone has been reported to result in better glycemic control with less variability of blood glucose concentration [10]. This may be clinically relevant as it has been demonstrated that an oscillating blood glucose level is associated with greater oxidative injury than sustained hyperglycemia [11]. Indeed, a number of reports indicate that glucose variability may be an independent predictor of outcome in critically ill patients [12]. A continuous infusion of glucocorticoid may, however, result in greater suppression of the hypothalamic-pituitary-adrenal axis. Furthermore, different glucocorticoids differentially affect gene transcription and have differing pharmacodynamic effects. Consequently, the preferred glucocorticoid and the optimal dosing strategy in patients with septic shock remain to be determined.

Evidence-based medicine is defined as the use of the best current scientific evidence in making decisions about the care of individual patients. Owing to the dearth of high-level evidence, it is not possible to make strong evidence-based recommendations on the use of glucocorticoids in patients with sepsis. Therefore, at this juncture, it is useful to summarize what we know, what we think we know, and what we do not know in order to
lay the foundation for future scientific exploration; this information is summarized in Table 1.

In summary, the risk/benefit ratio of glucocorticoids should be determined in each patient. A course (7 to 10 days) of low-dose hydrocortisone (200 mg/day) should be considered in vasopressor-dependent patients (dosage of norepinephrine or equivalent of greater than 0.1 μg/kg per minute) within 12 hours of the onset of shock [1]. Steroids should be stopped in patients whose vasopressor dependency has not improved with 2 days of glucocorticoids. While the outcome benefit of low-dose glucocorticoids appears to have a limited role in patients who have sepsis or severe sepsis and who are at a low risk of dying.

Table 1. Current knowledge concerning glucocorticoids in sepsis

| What we know |
|----------------------------------------------------------|
| • Sepsis causes complex alterations of the hypothalamic-pituitary-adrenal axis and glucocorticoid signaling [1]. |
| • Etomidate causes suppression of cortisol synthesis for up to 24 hours [13]. |
| • High random cortisol levels are a marker of disease severity and a poor prognostic marker [14]. |
| • Short-course, high-dose glucocorticoids are not beneficial in the treatment of severe sepsis/septic shock [15-17]. |
| • Treatment of septic shock with moderate-dose glucocorticoids for 7 days significantly reduces vasopressor dependency (adrenocorticotropic responders and non-responders) and intensive care unit length of stay [15-17]. |
| • Glucocorticoids do not increase the risk of superinfections [15-17]. |

| What we think we know |
|------------------------|
| • Glucocorticoids may reduce mortality in subgroups of patients with septic shock [15-17]. |
| • Glucocorticoids appear to be of no benefit in community-acquired pneumonia patients who are at a low risk of dying [7]. |
| • The addition of fludrocortisone does not appear to have additional benefits when treating patients with hydrocortisone [18]. |
| • Treatment with glucocorticoids may reduce the risk of post-traumatic stress disorder [19]. |

| What we do not know |
|---------------------|
| • Which patients with severe sepsis/septic shock should be treated with glucocorticoids? |
| • Should treatment with glucocorticoids be based on the results of a cosyntropin stimulation test? |
| • What is the treatment window? Twenty-four hours? |
| • How does one accurately diagnose adrenal insufficiency and inadequate cellular glucocorticoid activity? |
| • What is the optimal dosing schedule of glucocorticoids? |
| • Which glucocorticoid – methylprednisolone or hydrocortisone – should be used? |
| • Do glucocorticoids cause long-term myopathy? |
| • Do we need to treat a patient with glucocorticoids if he or she has received etomidate in the previous 24 hours? |

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Abbreviations

CORTICUS, Corticosteroid Therapy of Septic Shock.
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