

## Commentary

# The International Sepsis Forum's controversies in sepsis: corticosteroids should be used to treat septic shock

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### Abstract

The use of corticosteroids in septic shock remains controversial. It has been demonstrated that high doses of steroids (30 mg/kg methylprednisolone) for short periods of time are not beneficial. More recent studies using smaller doses (200–300 mg/day hydrocortisone) for longer periods of time have shown beneficial effects. These positive effects have included reversal of shock, trends toward decreased organ system dysfunction and decreased mortality. Based on the high proportion of patients who have relative adrenal insufficiency, the benefits of low doses of steroids and the minimal risks, steroids should be used to treat septic shock.

**Keywords** corticosteroids, relative adrenal insufficiency, septic shock, survival

In the early 1980s we were big proponents of using corticosteroids in septic shock, whereas in the late 1980s, following publication of the findings of the Veterans Administration Systemic Sepsis Cooperative Study Group on corticosteroids in sepsis [1] and those of the study of steroids in sepsis conducted by Bone and colleagues [2], we thought corticosteroids were a bad idea. In fact, subsequently, two meta-analyses [3,4] concluded that steroids were not beneficial in sepsis and septic shock. Based on recent data, there is enough evidence to suggest that we probably should be using corticosteroids in our septic shock patients. Although we support the use of steroids for treating septic shock, we clearly need a large trial in this area. In fact, we are starting a prospective, randomized, double-blind trial in Europe that will enroll large numbers of patients with septic shock (the CORTICUS study).

In 1984, our group showed [5] that there was a short period of time with a difference in mortality between a steroid-

treated group and a control group, and that there was a significant reversal in shock between the groups at 24 hours. We stated at that time that perhaps we should be giving steroids for a longer period of time rather than just two doses. This approach was likely to reverse shock in more patients and perhaps improve survival.

There has clearly been a change in thinking of how steroids should be used, in treating both septic shock and the acute respiratory distress syndrome. Older studies used large doses for short periods of time, and were given early in the treatment – typically one or two doses of methylprednisolone (30 mg/kg). This was often done before any organisms were identified, and hence using corticosteroids might be associated with an increased incidence of complications related to superinfections. However, more recent studies recommend smaller doses of steroids, used for longer periods and given even later in the course of the disease.

## Relative adrenal insufficiency

During septic shock there is an important problem of relative adrenal insufficiency. This causes adrenergic receptor desensitization – a decreased number of both  $\alpha$ - and  $\beta$ -adrenergic receptors. This is either related to sepsis itself or to the use of vasopressors for long periods of time. Corticosteroids may help with the resensitization of these receptors, leading to haemodynamic improvement – decreasing catecholamine requirements, reversal of shock and perhaps even reversal of organ system failure. All of these effects may decrease mortality.

Annane and colleagues [6] found the highest 28-day mortality (82%) in patients who had high baseline cortisol levels and who did not respond to adrenocorticotrophic hormone (ACTH) by increasing cortisol levels by greater than 9  $\mu\text{g}/\text{dl}$ . If one looks at relative adrenal insufficiency in terms of nonresponders to ACTH ( $\leq 9 \mu\text{g}/\text{dl}$ ), then the mortality in that group was 72%, whereas in those who did respond to ACTH the mortality was 32% – more than double. How common is relative adrenal insufficiency? In the study conducted by Annane and colleagues [6] it was 54%, but in some recent data there are suggestions that between two-thirds and three-quarters of patients with septic shock may have relative adrenal insufficiency. Therefore corticosteroids would be helpful in many patients.

Clinical data looking at the increase in mean arterial pressure after noradrenaline (norepinephrine) administration [7] show that there is a greater response to noradrenaline in patients with normal adrenal function than in those with impaired adrenal function. However, when one gives low doses of corticosteroids to patients with impaired adrenal function the responses to noradrenaline move closer together, so that there are no longer statistical differences in the noradrenaline effects of increasing blood pressure [7].

## Shock reversal

The prospective, randomized, double blind study conducted by Bollaert and colleagues [8] looked at 41 patients who required catecholamines for more than 48 hours and had been in shock for 5–6 days. By that time the patient's infectious organisms had most likely been identified and they were probably on appropriate antibiotics, so there were few problems in terms of complications of corticosteroids. Patients were given 100 mg hydrocortisone intravenously three times a day for 5 days. Treatment was discontinued if shock did not reverse. If shock reversed, then treatment was continued with half doses for 3 days and quarter doses for another 3 days and stopped. There was significant shock reversal at 7 days, and 28-day mortality showed a trend toward significance (63% versus 32%).

Briegel and colleagues [9] performed a prospective, randomized, double-blind, single-centre study in hyperdynamic septic shock patients. They enrolled septic

patients who were on vasopressors and had been in shock for at least 3 days. While on vasopressors, patients were given a bolus of 100 mg hydrocortisone or placebo, followed by a continuous infusion of 0.18 mg/kg per hour of hydrocortisone or placebo. In addition to a decreased mean time for shock reversal, there also seemed to be a trend toward decreased organ system dysfunction in the steroid-treated group as compared with the control group.

A multicentre, prospective, randomized, double-blind French study [10] involved 300 patients enrolled early after the onset of shock. Among nonresponders ( $\leq 9 \mu\text{g}/\text{dl}$  increase in baseline cortisol after ACTH), there was greater survival in the steroid-treated group as compared with the placebo group. Interestingly, there was a trend toward a higher mortality in those patients who were responders and treated with steroids. Therefore, it is important to evaluate corticosteroids in a larger group of patients, evaluating both responders and nonresponders.

In addition to efficacy, which is discussed above, safety is also important. The problems associated with corticosteroids occurred in those studies that used high doses (1–2 g methylprednisolone). When lower doses (200–300 mg/day of hydrocortisone) were used, superinfection and other complications were not observed. The one study that did have a complication was the study conducted by Briegel and colleagues [9]. Patients developed hyponatraemia and increased alanine aminotransferase levels at day 14. The hyponatraemia was probably related to the continuous infusion.

## Conclusion

What should one do at the present time? For routine use of low doses of corticosteroids in septic shock, there are minimal or no risks. There are data to suggest that relative adrenal insufficiency is a common problem in the majority of patients with septic shock. Therefore, physicians can reverse shock and improve survival with corticosteroids, as was shown in the prospective, double-blind study reported by Annane and colleagues [10]. One should be aware that, in the study by Annane and colleagues, patients were in septic shock with systolic blood pressure below 90 mmHg for more than 1 hour. This is not the usual patient because most respond to fluids and vasopressors within an hour.

In summary, in the typical septic shock patient, based on the data we already have, given the frequency of relative adrenal insufficiency in this population and the lack of a downside to the use of lower doses of corticosteroids, the routine use of corticosteroids is probably beneficial. If physicians do not want to use them early, then they should wait a few days so as not to worry about superinfection.

## Competing interests

PST received an honorarium from the International Sepsis Forum for helping to write this commentary.

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