

## Use of glucocorticoids in the treatment of severe sepsis: another example of the law of the pendulum?

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In 1911, Rupert Waterhouse described a case of shock in a child with severe sepsis, with adrenal bilateral haemorrhage reported as "suprarenal apoplexia" being found at autopsy<sup>1</sup>. From this report until the last recently published study on the utility of steroids in severe sepsis and septic shock<sup>2</sup>, the use or not of these drugs has remained controversial in the literature (Figure 1). The evidence observed to date in an excellent review<sup>3</sup> has shown that the use of corticosteroids has gone through several phases: initially used at high doses but now abandoned, and later at physiological doses justified by the scarce response to the corticotropin test in patients with septic shock.

Severe sepsis and septic shock are severe forms of presentation of infection which may cause suprarenal deficiency in almost half of the patients<sup>4,5</sup>. In addition, the body tissue may become resistant to steroids<sup>6</sup> by the development of fewer corticosteroid receptors or with low affinity receptors<sup>7-9</sup>. Some investigators have, therefore, analysed the physiological mechanisms of shock with the aim of undertaking potential interventions. The administration of corticosteroid could potentially benefit patients.

In an observational study carried out in Spain by Esteban et al. the incidence of severe sepsis and septic shock was 104 and 31 cases/100,000 inhabitants/year, with a mortality of 28% and 45.8%, respectively. These data may be superimposed to those published in the USA<sup>11</sup> and Europe<sup>12,13</sup>.

A systematic review carried out by Cochrane<sup>3</sup> on the use of steroids in severe sepsis and septic shock, included only studies comparing corticosteroids with standard treatment alone or with a placebo among the 16 relevant studies reviewed. Interestingly, on classifying the studies by year, almost all those undertaken before 1992 reported a risk of death at 28 days of greater than 1 while almost all the studies performed after this year describe a relative risk of less

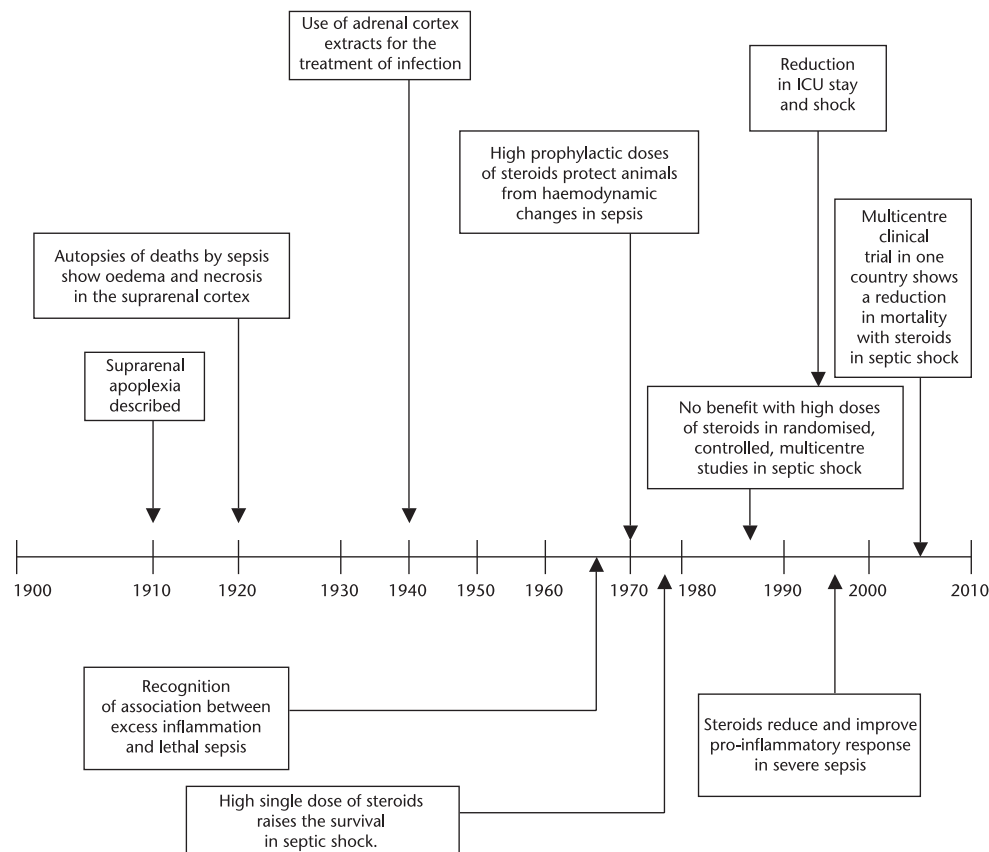
than 1. This year coincides with an agreement of the definitions of severe sepsis and septic shock<sup>14</sup>, with new comprehension of the role of the suprarenal glands in survival after septic shock<sup>3</sup>. In this review the conclusions drawn have implications for clinical practice. In general, corticosteroids had no impact on 28-day mortality by all causes or on intrahospital mortality by severe sepsis or septic shock. A meta-analysis of a subgroup of 5 trials<sup>15-19</sup> showed that a 5-day cycle of low dose corticosteroids led to a reduction in the duration of shock and an improvement in intra-intensive care unit survival, with no increase in adverse events (gastrointestinal haemorrhage or an increase in superinfections by corticoids). The dose used in these studies was of 200 to 300 mg of hydrocortisone (or equivalent) as an intravenous bolus of continuous infusion during 5 to 11 days. The tests accumulated in 8 studies<sup>20,21</sup> did not uniformly support the use of brief cycles with high dose corticosteroids for severe sepsis or septic shock. Some topics remain to be clarified in successive investigations including: i) definition of the criteria for suprarenal insufficiency in septic shock, ii) evaluation of the role of a prolonged cycle of low doses of corticosteroids to treat septic shock in children, iii) analysis of the prolonged use of a low dose of corticosteroids to treat severe sepsis, iv) determination of the optimum time to initiate treatment, the adequate dosage of hydrocortisone (or equivalent) and the duration and modality of treatment withdrawal, and v) the need to clarify the additional role of replacement of mineral corticoids in future studies.

In this setting the CORTICUS study for the treatment of septic shock with hydrocortisone, initiated in 2002 and recently published in January 2008, was carried out, being the reason for this editorial<sup>2</sup>. A randomised, double-blind, controlled multicentre study was carried out in adults with septic shock of at least 72 hours of evolution. After performing a

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**RECEIVED:** 9-6-2008. **ACCEPTED:** 13-6-2008. **CONFLICT OF INTEREST:** None.



**Figure 1.** History of the utility of corticosteroids in septic shock in the literature.

standard ACTH (250 µg) test, the patients received 50 mg iv of hydrocortisone or placebo every 6 hours (200 mg/d) during 5 days, with a progressive diminution in the doses during 6 more days. The main outcome analysed was 28-day mortality in patients without response to the ACTH test (relative suprarenal insufficiency, RSI). A sample size of 800 patients was calculated. The trial was prematurely suspended due to the slow recruitment of new cases and included only 499 patients. Of these, 46.7% had RSI and 65% of the patients recruited were surgical. No differences were observed in the mortality between hydrocortisone and placebo or in the total number of patients (34.3% with hydrocortisone and 31.5% with placebo; RR 1.09; CI 95% 0.84-1.41;  $p = 0.51$ ) or between the patients with RSI (39.2% with hydrocortisone and 36.1% with placebo;  $p = 0.69$ ). Shock reverted in less time among patients receiving hydrocortisone (3.3 versus 5.8 days with placebo), but more new episodes of infections were observed (33% versus 26%;  $p =$  not significant).

This is still not the definitive study on the efficacy or not of hydrocortisone in septic shock. This study has some important methodological limitations such as: premature interruption of recruitment due to lo-

gistic difficulties; the choice of the main objective focused only on the subgroup defined a posteriori (those who did not respond to the ACTH test); patients treated with etomidate (26%) which inhibits corticoid production by the suprarenal gland not being excluded, which may justify the high percentage of no response to corticotropin (76%); some patients received fludrocortisone, the effects of which are unknown, or the inclusion of patients in the study up to 72 hours after the onset of septic shock. On the other hand, the population included was not the same as that in previous studies and thus, the results do not invalidate previous studies, although they do question them: the results of this study do not support the use of hydrocortisone in septic shock and demonstrate the lack of utility of the ACTH test in selecting patients who may benefit from this treatment. However, the lower mortality of the patients in CORTICUS compared with the study by Annane et al. and the more favourable haemodynamic response in those treated with hydrocortisone suggests that the treatment may be beneficial in patients with a greater risk of death such as those who remain hypotensive, despite the initiation of vasoactive drugs or those requiring progressively greater doses of these drugs and have therefore been rec-

**Table 1.** 2008 recommendations of the Surviving Sepsis Campaign for the use of hydrocortisone in septic shock<sup>22</sup>**Degrees of recommendation evaluated according to the Grade system****Aggressor sex**

1. Consider the administration of hydrocortisone in adults with septic shock only when hypotension does not respond to adequate fluid replacement and the administration of vasopressors (2C).
2. The use of the ACTH test not recommended for selecting patients with septic shock who should receive hydrocortisone (2B).
3. Hydrocortisone is preferable to dexamethasone (2B).
4. Fludrocortisone (50 µg iv once a day) may be included if an alternative to hydrocortisone without activity, mineralocorticoid, is used. The use of fludrocortisone is optional if hydrocortisone is administered (2C).
5. Steroid treatment may be reduced when vasopressors are no longer necessary (2D).
6. The dose of hydrocortisone should not be greater than 300 mg/day (1A).
7. Do not use corticoids to treat sepsis in the absence of shock except if the patient has an endocrinologic history or one of the use of corticoids as recommended.

ommended in the recently updated guidelines of clinical practice for the treatment of severe sepsis and septic shock (Table 1)<sup>22</sup>.

Although the CORTICUS study could not define the role of corticosteroids in septic shock, the investigators have performed a valuable service. They remind us that few critical care practices or treatment recommendations are based on unequivocal tests and that, in some cases, a critical evaluation and an open mind may be more appropriate than unconditional adherence to guidelines<sup>23</sup>.

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