CHAPTER 7.

Should we abandon corticosteroids during septic shock? No

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Abstract

Purpose of review

With the publication of the results of the recent CORTICUS trial, stress ('low') doses of corticosteroids for the treatment of vasopressor-dependent septic shock in adults can still be considered controversial. The purpose of this narrative review is to elaborate the pros and cons of this treatment in clinical practice and to formulate clinical and research directions.

Recent findings

The recent CORTICUS study only shows a beneficial effect of stress doses of corticosteroids in the time interval to shock reversal and not on mortality, potentially explained by an increased risk for superinfection. The mortality in the placebo arm was relatively low and lower than in earlier randomized studies in which stress doses of corticosteroids had a favorable hemodynamic effect and conferred a survival benefit in septic shock.

Summary

Treatment by stress doses of corticosteroids should not be abandoned during septic shock. Additional studies are needed, however, to better delineate the patient group with the highest likelihood to benefit from this therapy, as a function of severity of illness, response to adrenocorticotrophic hormone testing or both. For now, results of the CORTICUS study should not change current clinical practice of administering 200–300mg of hydrocortisone daily (in divided doses) in case of fluid and vasopressorinsensitive septic shock and rapid tapering of this treatment on the basis of a hemodynamic response.

Introduction

Septic shock remains the most common cause of death in the intensive care unit, with mortality rates approaching 50%. Current guidelines for the treatment of this syndrome include consideration of therapy with stress ('low') doses of corticosteroids if the patient is poorly responding to repeated fluid challenges and on vasopressor therapy [1]. The guidelines indicate that this should not be tailored individually on the basis of an adrenocorticotrophic hormone (ACTH) test prior to start of therapy. In contrast, prior studies [2,3] had suggested the concept of relative adrenal insufficiency (RAI) or critical illness-related corticosteroid insufficiency (CIRCI), characterized by a subnormal response in circulating (total) cortisol upon a (supraphysiologic) ACTH stimulus and necessitating substitution therapy by stress doses of hydrocortisone (with or without the mineralocorticoid fludrocortisone) to improve outcome. However, the recent corticosteroid therapy of septic shock (CORTICUS) trial [4] has introduced uncertainty on the concept of RAI in septic shock as well as the beneficial effect of stress doses of corticosteroid on vasopressor responsiveness and outcome. Hence, the prediction by ACTH testing as well as the effect of stress doses of corticosteroids on hemodynamics and outcome remain controversial (Table 1 summarizing pros and cons), particularly in children in whom less data are available than for adults [5]. This narrative review therefore attempts to reconcile some recent and older studies on RAI and stress doses of corticosteroids for septic shock, to formulate clinical directives and to delineate future research issues.

Table 1 Pros and cons of stress doses of corticosteroids in septic shock

Pros	Cons
More rapid or frequent shock reversal	RAI is not identifiable and does not predict effect of corticosteroids
Mortality benefit in some studies on high-risk patients	Mortality benefit controversial
Effect most pronounced in patients with low cortisol increase upon ACTH, suggesting RAI	Elevated risk for superinfection
Pharmacological doses useful in specific infections	Elevated risk for critical illness myopathy
Useful when septic shock is complicated by ARDS	Hyperglycemia

ACTH, adrenocorticotrophic hormone; ARDS, acute respiratory distress syndrome; RAI, relative adrenal insufficiency.

Relative adrenal insufficiency, disease severity and benefit of corticosteroid therapy

Depending on definitions and studies, the rates of RAI in septic shock vary between 20 and 70% and associations with morbidity and mortality are variable [3]. The predictive value of the ACTH test result for hemodynamic compromise and amelioration thereof by stress doses of corticosteroids is unclear with some authors suggesting and others denying such association [3]. In recent retrospective studies [6–8], the lack of predictive value of ACTH test results on hemodynamic improvement and survival upon corticosteroid treatment in septic

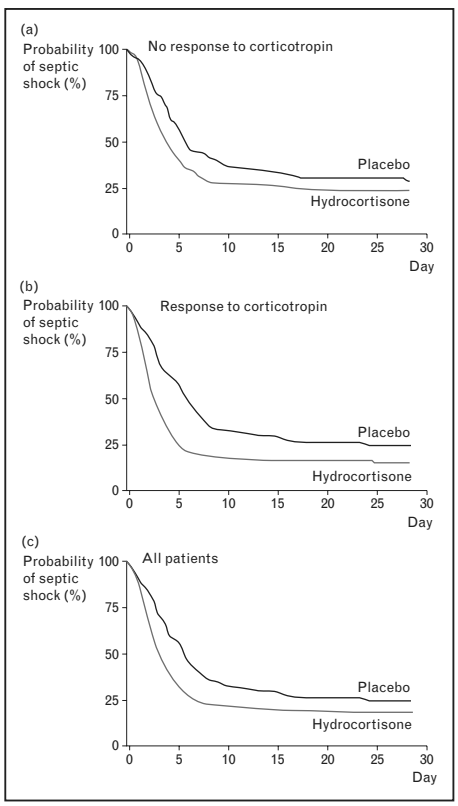
shock were again emphasized. Nevertheless, a subnormal response to metyrapone, blocking conversion of 11bdeoxycortisol to cortisol, helped to identify the less than 250 nmol/l or 9 μg/dl response to 250 μg of ACTH as evidence for RAI in severe sepsis and septic shock [9].

Indeed, it is the long-term controversy on RAI and corticosteroids in septic shock that prompted the CORTICUS trial [4]. CORTICUS is a double-blind randomized clinical trial, the largest one done so far. The primary end point was 28-day all-cause mortality in nonresponders (defined as an increase of less than 250 nmol/l or 9 μg/dl) in circulating cortisol upon a 250 μg ACTH test. Secondary end points dealt with mortality in the entire population, organ failure resolution, and safety. The study was conducted from 2002 to 2005 at 52 sites in Europe and the Middle East and 499 patients (of anticipated 800 with 50% mortality and 80% power to detect a fall by 10% in nonresponders) were included. Because of slow recruitment and other logistic reasons, the inclusion was stopped at 499 patients. Initially, patients with fluidrefractory septic shock or in need of vasopressor therapy (>1 h) were given 50mg of hydrocortisone every 6 h (starting up to 24–72 h after onset of shock) for 5 days with a tapering dose over the next 6 days, or placebo. Fludrocortisone was not administered. Groups were well balanced regarding baseline characteristics. All-cause mortality was similar between the two arms (34% corticosteroids vs. 31% placebo), irrespective of ACTH test results but lower than in the Annane et al. trial [2]. Mortality was somewhat but nonsignificantly higher in ACTH nonresponders. Overall, rates of shock reversal appeared more rapid in those patients given corticosteroids, particularly (paradoxically) in those patients responding to ACTH (Fig. 1).

The landmark study by Annane et al. in 2002 [2] suggested that the survival benefit of treatment by 200 mg hydrocortisone per day together with 50 mg of fludrocortisone vs. placebo, for 7 days in patients with vasopressor-dependent [dopamine above 5 μg/kg per minute or on (nor)epinephrine], fluid-refractory septic shock (of 3–8 h duration) was greatest in those patients showing a cortisol increment upon 250 μg of ACTH below 250 nmol/l or 9 μg/dl as evidence for RAI, even though the protocol was changed during the study and statistical significance was reached in some analyses after adjustment only. In patients with a higher cortisol increment upon ACTH, hydrocortisone or fludrocortisone treatment was even associated with a somewhat (but nonsignificantly) increased risk of death. The Annane et al. study [2] is in line with the earlier studies by Bollaert et al. [10], Briegel et al. [11], Yildiz et al. [12], Keh et al. [13], and Oppert et al. [14] showing immunologic, hemodynamic and survival benefits of hydrocortisone treatment in septic shock patients even if not subjected to or independent of ACTH test results. The mortality rates in the placebo arms of these studies varied from 25 to 63%, perhaps higher, on average, than in the CORTICUS trial [4]. The Annane et al. study [2] has not yet been reproduced, and is, up till now, only retrospectively

confirmed in 218 patients [15]. Indeed, de Jong et al. [15] demonstrated in a 'real life' study with a change in clinical practice after the Annane et al. trial [2] that the cortisol response to ACTH related to severity of disease and that a low (cortisol below 100 nmol/l or 3.6 μg/dl) rather than a higher increment was associated with a beneficial effect of hydrocortisone therapy on vasopressor sensitivity and outcome (reduction in mortality from 57 to 33%) in patients meeting septic shock criteria for about 6 h on the day of ACTH testing and start of corticosteroid therapy. Hence, it cannot be excluded that patients with greater disease severity and a high risk of death, thereby more likely to manifest high baseline cortisol values as a consequence of stress and relatively low increases upon ACTH, had more benefit from stress doses of corticosteroids than less severely ill patients. Finally, in a study [16] using historical controls, authors showed that septic shock in liver cirrhosis had a better survival rate if treated by stress doses of corticosteroids, particularly when the cortisol or ACTH test response was relatively low (including a cortisol increase below 250 nmol/l).

Figure 1 Kaplan–Meier curves of shock reversal vs. time for groups of patients with septic shock



Patients treated by hydrocortisone or placebo, without a response to ACTH (panel a), those responding to ACTH (panel b) and overall (panel c). It is shown that steroid treatment accelerated shock reversal, particularly ($P < 0.001$) in patients responding to ACTH. Reproduced with permission from [4**].

Why do the recent CORTICUS findings differ from earlier trials? First, compared with the report by Annane et al. [2], patients in this study were not as severely ill, and more severe (but not preterminal) illness may benefit more than less severe disease, as explained above [15]. The poor predictive value by ACTH test results for the effect of hydrocortisone treatment on speed of shock reversal and outcome in the CORTICUS study can also be explained by the relatively low disease severity of the patients in this study. The mortality rate in the Annane et al. trial approached 60 vs. 34% in CORTICUS. Also, the allowable duration of shock prior to inclusion was shorter in the Annane et al. study [2] that is 3–8 h vs. up to 24–72 h (the latter after protocol amendments) after onset of shock in the CORTICUS trial. It is likely that only patients at a high risk of death will benefit from stress doses of corticosteroids and this benefit will be reduced with a delay in starting treatment. The severity of shock and support by infused vasopressors were less in the CORTICUS trial by virtue of inclusion criteria. The Annane et al. study had a preponderance of respiratory and the CORTICUS study of abdominal infections, and cortisol/ACTH test results may be less predictive in the latter [8]. Finally, there was some difference owing to the withholding of fludrocortisone in the CORTICUS as opposed to the Annane et al. study, owing to the fact that CORTICUS encouraged physicians to follow sepsis guidelines, or owing to different durations of therapy (11 vs. 7 days) and increasing side effects with prolonged administration.

Disease severity was expressed by the simplified acute physiology score (SAPS) II score in the de Jong et al. study [15], but how stratification should be done to identify patients most likely to benefit from corticosteroids remains open for future study. Given the varying ACTH test result cutoff levels in the literature [2,3,15] predicting the highest likelihood of a response to corticosteroids, stratification could also be done, for instance, on the basis of scoring systems and doses of vasopressor therapy needed to maintain blood pressure. In any case, results of ACTH testing seem fairly concordant with severity of disease estimates [15], so that stratification on the basis of the perhaps unphysiological and poorly reproducible ACTH test may not be necessary.

The results of the CORTICUS trial can be added to meta-analyses of other published prospective studies and may diminish the statistically significant survival benefit of treatment by stress doses of corticosteroids in these analyses [17]. Indeed, when one looks carefully at all randomized controlled trials (accounting for 2700 patients before the CORTICUS trial), one can draw the following conclusion: a relatively long course (5 days or more at full dose) of daily stress doses (300mg or less of hydrocortisone or equivalent) improves survival [relative risk (RR), 0.87; 95% confidence interval (CI) 0.76–0.99]. They reduce 28-day, hospital and intensive care unit mortality (four trials, n¼425, RR 0.83, 95% CI 0.70–0.97) by increasing shock reversal by day 7 and 28 (four trials, n¼425, RR 1.26, 95% CI 1.04–1.52), without increasing the rate of gastroduodenal bleeding (10 trials, n¼1321, RR 1.16, 95% CI 0.82–1.65) [16]. Negative

retrospective or nonrandomized studies were not yet incorporated in these meta-analyses.

Special circumstances

Other considerations may affect decisions to administer corticosteroid in patients with septic shock. In patients with chronic obstructive lung disease, mechanically ventilated for pneumonia, for instance, pharmacological doses of corticosteroids may have to be administered to alleviate bronchospasms. In septic shock patients intubated with help of etomidate that may suppress adrenocortical function and cortisol synthesis for 24–72 h even after a single dose and may constitute a risk factor for death [18], as found in the CORTICUS study [4] also, the decision to administer hydrocortisone may be taken relatively early. This may also apply to patients on steroids prior to development of septic shock. There are some infectious disease states that may particularly benefit from treatment by corticosteroids in pharmacological doses [19]. These include typhoid fever and bacterial meningitis in children and adults [20,21]. Patients having septic shock in the course of these diseases should therefore receive high and not the stress dose corticosteroids. In severe typhoid fever, corticosteroid therapy may attenuate mortality and in proven bacterial meningitis they may decrease hearing loss and other neurological sequelae as well as mortality [20,21,22]. Finally, patients (n=46) with communityacquired pneumonia (CAP) admitted to the intensive care unit may have a somewhat lower morbidity and mortality, if treated by hydrocortisone, as compared with placebo [23]. Hence, clinicians may wish to start corticosteroids earlier in septic shock patients with CAP. During mechanical ventilation, stress doses of corticosteroids in low ACTH responders may facilitate weaning, but most of these patients had pneumonia or sepsis [24]. Hence, corticosteroids in septic shock should perhaps not be tapered when a concomitant weaning trial is initiated, even though prolonged use may increase the risk for superinfections and myopathy. Similarly, postoperative hydrocortisone therapy may reduce bouts of atrial fibrillation after cardiac surgery [25], but, again, it is unclear how this would interact with (treatment for) shock, in patients developing sepsis after cardiac surgery, for instance [26]. Only when complicated by sepsis and shock, burn injury patients may benefit from stress doses of corticosteroids [27,28].

The treatment of acute respiratory distress syndrome (ARDS), early after onset, by corticosteroids (methylprednisolone 1 mg/kg per day which may be equivalent to 300mg of hydrocortisone) may not remain controversial [29], particularly after the recent trial by Meduri et al. [30]. In this trial, early treatment reduced ventilation duration and mortality in 63 treated patients vs. 28 controls, 66% having sepsis and some of them even septic shock. The treatment was not complicated by superinfections. Hence, in patients with septic shock complicated by ARDS, a frequent combination, the practicing physician has to choose

between prednisolone and hydrocortisone, in the absence of a direct comparison. Annane et al. [31] showed a mortality benefit in a post-hoc study of the landmark trial on septic shock particularly in those patients with ARDS (as opposed to those without ARDS) nonresponding to ACTH, by treatment with hydrocortisone and fludrocortisone. The current level of evidence thus suggests that stress doses of corticosteroids may suffice in treating patients with septic shock and early ARDS.

Mechanisms of action and adverse effects

Stress doses of steroids might act in septic shock by improving vessel wall sensitivity to circulating or Corticosteroids in septic shock Groeneveld et al. 387 exogenously administered vasoactive drugs, by downregulating expression of vasodilating inducible nitric oxide synthase, by suppressing immune responses, and others, but the precise interplay of factors is still conjectural [14]. In vivo, the sensitivity of the vessel wall may improve after corticosteroid administration [32]. Obviously, these potential benefits may be offset, particularly in less severely ill and hemodynamically compromised patients by adverse effects on immunology and metabolism. Corticosteroid therapy, even when given in stress doses may carry adverse effects such as hyperglycemia and immunosuppression, potentially inducing or aggravating critical illness myopathy and increasing risks for infections [33,34]. In the hydrocortisone-treated group in the CORTICUS trial [4], there was an increased incidence of superinfections (34 vs. 27%, P¼0.099), including new episodes of sepsis or septic shock, with combined odds ratio of 1.37 (95% CI 1.05–1.79). Hyperglycemia was also more common on study days 1–7 in patients treated by corticosteroids. Hyperglycemia may be attenuated, however, when giving corticosteroids as a continuous infusion rather than as a bolus infection [11,35]. In the metaanalysis by Annane et al. [17], however, rates of superinfection (12 trials, n¼1705, RR 0.93, 95% CI 0.73–1.18) and of hyperglycemia (six trials, n¼608, RR 1.22, 95% CI 0.84–1.78) were not increased in corticosteroid vs. placebo-treated patients. In the study by Meduri et al. [30], myopathy, superinfections and hyperglycemia were also not more frequent in the methylprednisolone group.

Too wide application of corticosteroids, for example, for trauma and hemorrhagic shock in surgical patients may be associated with more adverse effects than benefits [33,36]. Hence, stress dose corticosteroid therapy in the critically ill should be limited to the clinical circumstances mentioned and broader application, even in medical patients, may be harmful [33,36].

Conclusion

On the basis of the foregoing, and in spite of the negative CORTICUS trial, we still recommend a 5–7-day course of stress doses of hydrocortisone to increase (or speed) shock reversal and survival in patients with fluid-refractory, vasopressor-dependent septic shock, if initiated relatively early (within hours after onset of shock). The best available clinical evidence is that stress doses of corticosteroids result in more rapid shock reversal. It is likely that the sickest patients, such as those poorly responsive to ACTH, fluids and vasopressors, are more likely to benefit from hydrocortisone, and that the hemodynamic response in these patients is more likely to influence mortality than in patients rapidly stabilized with fluids or vasopressors. Together with dose–response relationships of the corticosteroids administered, the role of mineralocorticoids, and the subgroups of septic shock patients likely to benefit most, this should be the subject for further study. After shock reversal, hydrocortisone should be rapidly tapered.

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