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Should We Use Corticosteroids in Sepsis? An Evidence-Based Approach

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Abstract

Almost every organ systems are affected by conditions inflicted by sepsis and septic shock (S&SS). Therefore, evidence-based approaches coupled with a system-based rationale are the prerequisites to diagnose and treat patients.

Many factors modulate cortisol metabolism in chronic severe disease states and thus, adrenal insufficiency are seen commonly in the involved patients. There is an on-going debate on the favorable effects of administration of low-dose corticosteroids in those with S&SS, particularly 200 to 300 mg hydrocortisone was claimed to improve clinical outcomes in sepsis. The main rationale of glucocorticoid administration in sepsis is to restore hypothalamic-pituitary-adrenal axis (HPAA), equilibrium and homeostasis again.

Although management strategies which target hemodynamic stabilization with their foci on fluid and vasopressor administration appear to be standard, these should be individualized. Treatment regimens including corticosteroids were associated with a small but significant reduction in mortality and improvement of neuromuscular weakness. Therefore, the current guidelines published a weak recommendation favoring CST administration. Finally, individualized treatment options should be tailored for each patient with regard to hemodynamic properties, age and physiological reserves, anticipation of adverse effects, and alternative regimens for management.

Keywords: Corticosteroids; Sepsis; Septic Shock; Treatment

Corticosteroids (CST)

Hypothalamus triggers synthesis of corticotrophin releasing hormone (CRH) in response to stimulants in accord with threatened homeostasis, which, in turn, starts release of ACTH from anterior pituitary gland. ACTH stimulates adrenal glands to release cortisol and derivatives. Thus, cortisol is the effector molecule of the hypothalamic-pituitary-adrenal axis (HPAA), and CRH and ACTH are hormones which induce its release in a sequence.

Failure of SIRS (systemic inflammatory response syndrome) criteria to diagnose and predict sepsis and septic shock (S&SS) is demonstrated in the recent years. On the other hand, [Sequential (sepsis-related) organ failure assessment] (SOFA) criteria are shown to have a higher accuracy in prediction of the outcome of the septic patient. Tissue damage in general is closely linked to the insufficiency of tissue oxygenation. Many organ systems are affected concurrently by conditions inherent to S&SS. Therefore, evidence-based treatment approaches assume a system-based rationale to improve the clinical course of the patients.

Methods

This article is a review of the most recent literature to analyse consequences, and intended effects associated with corticosteroids in patients with S&SS. Online database searches were performed for randomized controlled trials, systematic reviews and meta-analyses published in the last twenty years till June 2019. The search terms included corticosteroids, sepsis, septic shock, treatment. Papers were examined for methodological soundness before being included.

Main strategies to mitigate organ dysfunction and mortality in sepsis include expedient and appropriate antimicrobial treatment, correction of tissue perfusion and prompt source control [1].

Corticosteroids and sepsis

Random serum cortisol (RSC): Total amount of cortisol fluctuates substantially in patients with SS. Many researches showed that both low and supranormal levels of RSC levels are associated with a boost in mortality [2,3].

Free cortisol: Protracted, chronic and critical illness leads to a reduction of cortisol binding globulin (CBG) in the circulation, and thus, levels of free cortisol rise. Therefore, free cortisol levels are put forth as a more accurate marker of HPAA, instead of RSC [4].

Activation of HPA axis: Normal RSC levels lie between 5 and 24 mcg/dL, and have a circadian rhythm [5] HPAA is activated in circumstances under physiological stress (operation, trauma, severe infections, hypotension/hypovolemia) and the circadian variations are erased [6,7]. RSC is raised to 40 to 50 mcg/dL [6,8,9].

Factors modulating cortisol metabolism in chronic severe disease states

- Prolonged half-life of circulating cortisol due to renal dysfunction
- Declined rate of cortisol breakdown [9].
- Reduced levels of albumin and CBG and resultant increase of free cortisol [8,10].
- Increased effectiveness of cortisol in response to cytokines' impacts in the tissue [8,11].
- Certain drugs in the routine use (i.e., ketoconazole, fenitoin, and etomidate) suppress the synthesis of cortisol, although the net effect in the clinical status and outcome of the patient is debatable [12].
- A number of hazardous factors such as utilization of CNS depressants, hemorrhage in the adrenal glands, malignant disease, and pituitary infarction impair the activity of HPAA.

Adrenal insufficiency (AI): How can I recognize it?

It is not an easy task to identify AI and "relative" AI in the critical patient. A change in the basal cortisol level (BCL) obtained one hour after the administration of 250 mcg cosyntropin less than 9 mcg/dL and RSC <10 mcg/dL are accepted as the requested criteria for AI [13].

Free cortisol levels are more accurate to highlight the adrenal functioning when compared to plasma or serine levels [4]. Patients with sepsis have 7 to 10 times greater free cortisol levels than the others and this is not affected by hypoalbuminemia.

In accord with a prospective study, BCL <10 mcg/dL and maximum cortisol increase below 9 mcg/dL, coupled with free cortisol <2 mcg/dL following methyrapone stimulation test should predict AI [14].

High-dose ACTH test yields substantially variable findings in cases with SS. In a study on 189 patients with SS high-dose ACTH test produced findings demonstrating a strong predictive value for 28-day mortality, that is, a short corticotropin test showed a good prognostic value in detecting patients with SS at high risk for death [15]. Accordingly, laboratory results indicating BCL above 34 mcg/dL and maximum cortisol increase below 9 mcg/dL will predict 82% risk of death.

Peaked stress is closely associated with reductions of cortisol metabolism and augmented release of cortisol [9]. One of the major endocrine debates in patients with SS is whether use of steroids is justified against adrenal suppression in those with glycemic control. In brief, CST should be administered when a patient in need of vasopressor treatment is thought to have adrenal suppression.

There is an on-going debate on the favorable effects of administration of low-dose CST, particularly 200 to 300 mg hydrocortisone was put forth to have the potential to improve clinical outcomes in sepsis.

As a general rule, hypotensive patients despite vasopressor treatment or those with RSC below 15 mg /dL can be given 200 mg hydrocortisone in 24 hours empirically [8]. Although these guidelines are still respected, CORTICUS [16] and HYPRESS studies [17] have mitigated this enthusiasm at least partially. A Germany-based randomized clinical research study (HYPRESS) in 2016, recruited all septic patients without shock states in 34 centers for 4.5 years (n=380) and randomized them for CST or placebo [17]. The patients receiving 200 mg hydrocortisone were not different in terms of mortality rates when compared to placebo group in 6 months' follow up.

In a recently published meta-analysis, Gibbison, *et al.* [18] postulated that hydrocortisone administration was associated with a reduced time interval until the reversal of shock, but this beneficial effect was not translated into a more favorable mortality figure.

Treatment with glucocorticoids

The main rationale of glucocorticoid administration in sepsis is to restore HPAA equilibrium and homeostasis again.

Although some outstanding researches such that CORTICUS and ADRENAL demonstrated that hydrocortisone treatment resulted in a shorter time to rescue the patient from sepsis, another study named APROCCHSS showed that co-administration of fludrocortisone with hydrocortisone was associated with a reduction in mortality in 90 days [19]. Fludrocortison (50 mcg via gastric tube, once a day) can be given as an accompaniment of hydrocortisone. Under the light of these information, most authors suggest that it is reasonable both administering CST and withholding them in sepsis [20]. Table 1 summarizes the phases approach in management of septic shock.

A large-scale study published in 2002 reported that 50 mg hydrocortisone qid accompanied by 50 mg fludrocortisone daily resulted in a change of 28-day mortality from 63% to 53%, while those with adequate adrenal reserves have not a significant mortality benefit [21].

	Aim of treatment	What to monitor?
Rescue (minutes/hours)	Resuscitation and life support via fluids and vasopressors to provide adequate tissue perfusion	Vital signs monitoring, estimation of volume status
Improvement and/or optimization (hours)	Improving hemodynamic state to halt progression of organ failures	Echocardiography, ultrasonography, intraarterial catheters, central venous pressure monitoring
Stabilization (days)	Maintenance of circulatory stability, Prevention and treatment of adverse effects	Same as the previous phase
De-escalation (weeks)	Weaning from vasopressors and disposal of congestion/ edema fluid	Gradual cessation of invasive monitoring should patientsremain stable

Table 1: The management of septic shock

"The Corticosteroid Therapy of Septic Shock (CORTICUS)" study was published in 2008 as a multicenter, randomized, controlled double-blind design research and thus provided concrete data on the subject [16]. The centers recruited 499 patients with SS and randomized them to treatments with either IV hydrocortisone or placebo. They reported that hydrocortisone led to shorter time intervals for improvement in patients rescued from SS regardless of the response to corticotropin stimulation, without a higher rate of rescue from SS.

In a retrospective before-after comparison study published in 2017 by Marik, *et al.* administered IV vitamin C + hydrocortisone + thiamine to S&SS patients in ICU [22]. SOFA scores were found to be lower in the treatment group and, mortality rate was 8.5% vs 47%, favoring the treatment. Mean vasopressor infusion time was shorter with the treatment; 18 +-9 hours vs. 55+-28 hours. The authors cited that it may be efficient to administer IV vitamin C (6 gr/day) + hydrocortisone (50 mg x4/day) + thiamine (200 mg x2/day) to patients with S&SS in the early phase of the disease in prevention of progressive organ failures.

ESICM consensus report on "Critical Illness-Related Corticosteroid Insufficiency (CIRCI)" was updated lastly in 2017 [13]. They do not recommend administration of CST for septic patients not in SS (moderate level of evidence). In this report, 1 mg/kg/day methylprednisolone was recommended for patients with early phase of moderate-to-severe ARDS (moderate level of evidence). Patients in SS who do not response fluid resuscitation and vasopressor infusion were recommended to receive IV hydrocortisone no less than 400 mg/day, for at least 3 days (low level of evidence).

The recent ADRENAL study noted that 3658 patients diagnosed with SS were randomized to hydrocortisone or placebo and there was no significant difference in 90-day mortality [23]. In another milestone study, Rochwerg *et al.* conducted a meta-analysis on critical septic patients in 2018 and revealed that administration of CST was associated with a small but significant reduction in mortality and a concurrent mitigation of neuromuscular weakness to some extent [24].

So far, a huge number of researches published in the recent decades have failed to launch a breakthrough regimen capable of modulating the bodily response to sepsis. CST treatment can be an exception on this [25].

Conclusion

In conclusion, there is an everlasting search for optimal treatment regimen in sepsis. Although management strategies which target hemodynamic stabilization with their foci on fluid and vasopressor administration appear to be standard, these should be individualized. Treatment encompassing CST was associated with a small but significant reduction in mortality and improvement of neuromuscular weakness; this is why the current guidelines remark on a weak recommendation favoring CST administration. Individualized treatment options should be tailored for each patient with regard to hemodynamic properties, age and physiological reserves, anticipation of adverse effects, and alternative regimens for management.

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