Corticosteroids for septic shock

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Objective: **To gather the data to provide a rationale for using replacement therapy with hydrocortisone in septic shock patients.**

Data Sources: **The Medline and the Cochrane Library databases.**

Study Selection: **Studies in animals and in humans were considered when significant data were available about the mechanisms of action of corticosteroids or about their use in severe sepsis.**

Data Summary: **Corticosteroids were the first anti-inflammatory drugs tested in septic patients. Randomized trials clearly showed that a short course of a large dose of anti-inflammatory steroids is ineffective and potentially harmful in patients with severe sepsis. Recent demonstrations of altered hypothalamic-pituitary-adrenal axis response to septic insult have led to a reappraisal of the use of steroids in septic shock. Randomized trials in catecholamine-dependent septic shock patients strongly suggest that replacement therapy with hydrocortisone may alleviate the symptoms of systemic inflammatory response, reduce the duration of shock, and favorably affect survival.**

Conclusions: **Current evidence that the therapeutic interest of replacement therapy with corticosteroids increases suggests that low doses of hydrocortisone should be offered to patients with catecholamine-dependent septic shock. (Crit Care Med 2001; 29[Suppl.]:S117–S120)**

KEY WORDS: septic shock; adrenal insufficiency; catecholamine; corticosteroids; experimental studies; clinical controlled trials

Corticosteroids were proposed to treat patients with severe sepsis as early as 1940 (1). However, after an initial enthusiasm, several well-conducted randomized controlled trials cast serious doubts on the usefulness of steroids for the treatment of severe sepsis. A summary of all available randomized controlled trials performed between 1966 and 1993 was provided in two systematic reviews, which recommended that the use of high-dose corticosteroids to treat patients with severe infection be abandoned (2, 3). Nonetheless, a doubt still persists regarding the efficacy of a strategy of replacement therapy in catecholamine-dependent septic shock. This strategy relies mainly on the concept that septic shock may be complicated by an occult adrenal insufficiency and/or a peripheral glucocorticoid resistance syndrome.

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Concepts of Occult Adrenal Insufficiency and of Peripheral Glucocorticoid Resistance Syndrome

In sepsis, the hypothalamic-pituitary-adrenal (HPA) axis is activated through systemic and neural pathways. Circulating cytokines, like tumor necrosis factor α (TNF-α), interleukin (IL) 1, and IL-6, activate the HPA axis independently and, when combined, have synergistic effects (4). In plasma, IL-6 is sought to be the major determinant of the individual variation of HPA axis responses to lipopolysaccharide (LPS), activating vagal afferents at the level of the brain stem (5). The second pathway uses the neural routes of communication between the site of inflammation and the brain. Indeed, the interruption of the vagus has been shown to blunt the HPA axis and fever responses to intravenous challenge with LPS, TNF-α, or IL-1β, albeit elevated circulating cytokine levels (6, 7).

Since the Waterhouse (8) and Friderichsen (9) observations of bilateral hemorrhage of the adrenal glands, numerous experimental and clinical investigations have observed reversible dysfunction of the HPA axis during sepsis (10). In a prospective inception cohort study of 189 patients who had septic shock, thorough analyses demonstrated that the best definition of occult adrenal insufficiency should be based on a cortisol increment after a short corticotropin test of less than 9 μg/dL (11). Using this definition, the prevalence of occult adrenal insufficiency in severe sepsis was estimated at about 50%, and the 28-day mortality rate at about 75% (11). In addition, studies of mean arterial pressure responses to stepwise incremental doses of norepinephrine showed a rightward shift of the dose-response curve in septic shock patients who had occult adrenal insufficiency as compared with patients who had normal response to the short corticotropin test (12). These findings suggested that impaired adrenal function accounts, at least in part, for the vessels' decreased sensitivity to norepinephrine in severe sepsis.

A peripheral glucocorticoid resistance syndrome may occur in patients with septic shock and may be responsible for excessive immune-mediated inflammation as in rheumatoid arthritis, corticosteroid-resistant asthma, acquired immune deficiency syndrome (AIDS), and chronic degenerative osteoarthritis (4). In septic shock, the sensitivity of peripheral blood mononuclear cells to corticosteroids is generally up-regulated (13). However, several cytokines, like IL-2 and IL-4, induce an overexpression of nuclear factor κB (NF-κB) that alters the glucocorticoid receptor function (14, 15). Indeed, a decreased affinity of the glucocorticoid re-

ceptor was shown in peripheral blood mononuclear leukocytes from patients with sepsis or septic shock (16).

The two features of the HPA axis disruption parallel the intensity of inflammation, and have led to a renewal of interest in the use of corticosteroids in sepsis.

Replacement Therapy with Hydrocortisone and the Systemic Inflammatory Response to Sepsis

Mechanisms of Action of Corticosteroids. Cortisol opposes virtually all of the links of the inflammatory chain. Indeed, cortisol freely penetrates the plasma membrane of inflammatory cells, and binds to the glucocorticoid receptor (GR), which, in its inactive form, is linked to heat shock proteins (17). The binding of cortisol to the GR results in the dissociation of the heat shock protein subunits and exposure of DNA binding sites. The cortisol-GR complex penetrates into the nucleus to interact with specific DNA sequences (glucocorticoid-responsive elements) within the promoter regions of various genes. So, the activated complex interacts with the nuclear factor-IL-6 (NF-IL-6) enhancing the transcription rate for acute phase reactants (18) and with the activator protein-1 (AP-1) (19, 20) and the NF-κB (21, 22), inhibiting the synthesis of various pro-inflammatory factors. The activated cortisol-GR complex also induces IκBα expression which, in turn, sequestrates NF-κB dimers in the cytoplasm (14, 15). Then, cortisol prevents the migration of inflammatory cells from circulation to tissues by blocking the synthesis of chemokines (23), the synthesis of almost all pro-inflammatory cytokines including several interleukins (IL-1, IL-2, IL-3, IL-6), interferon-γ, granulocyte macrophage colony-stimulating factor, and TNF-α (4), but cortisol also enhances the production of the macrophage migration inhibitory factor (24). Furthermore, by stimulating the synthesis of lipocortin-1 (25), cortisol inhibits phospholipase A_2 and, subsequently, the arachidonic acid cascade. Finally, cortisol inhibits the synthesis of cyclooxygenase-2 (COX-2) (26, 27) and inducible nitric oxide synthase (iNOS) (28, 29).

Experience with Low Doses of Hydrocortisone in Sepsis. Low doses of hydrocortisone were shown to reproduce most of these effects in healthy subjects challenged by endotoxin (30–32) and in septic patients (33, 34). In healthy subjects, hydrocortisone (3 μg/kg/min for 6 hrs), administered immediately before or concomitantly to endotoxin exposure, prevents LPS-induced raises in temperature, heart rate, peak plasma levels of epinephrine, C-reactive protein and TNF-α, but not of IL-6 (30). When hydrocortisone was administered 12 to 144 hrs before endotoxin exposure, circulating levels of TNF-α and IL-6 were higher than those observed with endotoxin alone, suggesting that withdrawal of hydrocortisone induced a rebound of pro-inflammatory cytokines in plasma (Table 1). Subsequent experiments in healthy volunteers challenged with endotoxin have shown that hydrocortisone enhances the release of the anti-inflammatory cytokines IL-1 receptor antagonist, soluble tumor necrosis factor receptor (31), and IL-10 (32). In septic shock patients, intravenous hydrocortisone (~300 mg for 5 days) turned down the systemic inflammatory response syndrome, i.e., decreased core temperature, heart rate, and plasma levels of phospholipase A_2 and C-reactive protein (33). In addition, hydrocortisone infusion was associated with a decrease in plasma levels of pro-inflammatory cytokines, of nitrite/nitrates, and of soluble adhesion molecules (34). In septic shock, the discontinuation of hydrocortisone led to an amplified systemic inflammatory response syndrome, and to a new administration of vasopressors to maintain cardiovascular stability (33, 34).

Replacement Therapy with Hydrocortisone and Cardiovascular Function in Sepsis

Mechanisms of Action of Corticosteroids. Cortisol is known to contribute to blood pressure regulation (35), and hypotension is a common feature of adrenal insufficiency. Cortisol is also known as a determinant of cardiovascular tolerance to endotoxin (36), and vascular insensitivity to catecholamines is more marked in septic patients with occult adrenal insufficiency (12). Studies in dogs and cats have demonstrated that the vasoconstrictor response to epinephrine is enhanced by cortisol and aldosterone (37). In Wistar rats, administration of the corticosteroid antagonist RU 486 induced a 20 mm Hg drop in mean arterial pressure with unchanged cardiac output, depicting the role of cortisol on maintaining systemic vascular resistance (35). This study also showed that corticosteroids regulate vascular responses to norepinephrine and angiotensin II, but not to vasopressin. For example, the pretreatment with RU 486 blunted the angiotensin II induced raise in renal vascular resistance. These effects were not due to any mineralocorticoid activity, as shown by unchanged urinary sodium excretion and sodium balance. Moreover, as the administration of corticosterone restored mean arterial pressure, these effects were more likely to result from a glucocorticoid activity. Experiments showing that cortisol administration is associated with unchanged or even suppressed sympa-

Table 1. Summary of anti-inflammatory and cardiovascular effects of low doses of hydrocortisone in humans

Anti-Inflammatory Effects	Cardiovascular Effects
In healthy volunteers challenged with endotoxin	
Prevents fever, tachycardia, the raise in plasma levels of epinephrine, of C-reactive protein, of TNF-α; promotes the release of IL-1ra, sTNF-R, and IL-10; withdrawal of hydrocortisone induces a rebound in inflammation	Prevents endotoxin induced venous insensitivity to norepinephrine, independently of the iNOS or COX-2 pathways
In septic shock patients	
Decreases core temperature and heart rate; decreases plasma levels of phospholipase A_2, C-reactive protein, TNF-α, IL-1β, IL-6, nitrite/nitrate, and soluble adhesion molecules; withdrawal of hydrocortisone induces a rebound in inflammation	Increases mean arterial pressure and systemic vascular resistance; improves mean arterial pressure responses to norepinephrine and phenylephrine; decreases the time to cessation of vasopressors; decreases the duration of shock; withdrawal of hydrocortisone induces a relapse of shock

COX-2, cyclooxygenase 2; IL, interleukin; iNOS, inducible nitric oxide synthase; sTNF-R, soluble tumor necrosis factor receptor; TNF, tumor necrosis factor.

A short course with high doses of corticosteroids should not be administered in severe sepsis, except for specific entities like severe typhoid fever, Pneumocystis carinii *pneumonia in acquired immunodeficiency syndrome, or bacterial meningitis in children.*

thetic activity ruled out the role of the sympathetic system in cortisol-induced hypertension (38). Other experiments have suggested that this effect may result from iNOS or COX-2 inhibitions (39, 40). Thus, it appears that the precise mechanisms by which corticosteroids regulate cardiovascular homeostasis remain incompletely understood.

Experience with Low Doses of Hydrocortisone in Sepsis. In human volunteers challenged with local instillation of endotoxin, a pretreatment with 100 mg of hydrocortisone administered orally 2 hrs before the endotoxin challenge prevented the endotoxin-induced venous hyporesponsiveness to norepinephrine (41). This protective effect of hydrocortisone was not mediated through iNOS or COX-2 inhibitions. In patients who have septic shock and occult adrenal insufficiency, pressure response to norepinephrine is strongly impaired (12). In these patients, 50 mg of hydrocortisone administered as an intravenous bolus restored almost fully the mean arterial pressure response to norepinephrine. In addition, as compared with healthy volunteers, in septic shock, a 50-mg intravenous bolus of hydrocortisone slightly and similarly increased baseline mean arterial pressure, and increased more markedly the maximal theoretical effect of phenylephrine (E_{max}) (42). Hydrocortisone, in patients and in controls, did not affect ED_{50} (the dose of phenylephrine for which an effect of 50% of E_{max} was achieved). Finally, in patients, hydrocortisone tended to normalize the shape of the dose-response curve. These effects were not related to changes in baroreflex sensitivity, sympathetic or renin-angiotensin system activation, or nitric oxide (Table 1).

In two randomized trials (43, 44), short courses of large doses of corticosteroids induced a significant rise in blood pressure, and, in one of these studies (44), reversal of shock was achieved in 58% of patients treated by corticosteroids as compared with 38% of those receiving the placebo. However, treatment discontinuation was followed by the regression of these positive effects. Four small placebo-controlled randomized trials showed that in patients with catecholamine-dependent septic shock, a prolonged treatment (3 days or more) with low doses (about 300 mg daily) of hydrocortisone rapidly increased systemic vascular resistance and mean arterial pressure and did not affect cardiac output (34, 45–47). Simultaneously, as compared to placebo, in the hydrocortisone group, the median time to cessation of vasopressors was dramatically decreased: 4 vs. 13 days in one study (45) and 3 vs. 7 days in another (46).

Replacement Therapy with Hydrocortisone and Survival from Septic Shock

As early as 1963, a placebo-controlled randomized trial was performed to test the efficacy of hydrocortisone in decreasing doses (from 300 mg to 50 mg) for 6 days (48). This study did not show any beneficial effects of hydrocortisone in patients with severe sepsis. However, several pitfalls must be stressed: (1) the study population consisted of children and adults, (2) a large number of patients had meningitis, (3) the two groups were unbalanced for the type of infection with more fulminant staphylococcal infections in the hydrocortisone group, and (4) the distribution of prognostic factors, the appropriateness of antibiotic therapy, and supportive care were unknown. Therefore, the results of this old study cannot be applied readily to septic patients treated at the present time. Almost 20 yrs later, in a quasi-randomized trial in 18 critically ill patients with presumed adrenal insufficiency, hydrocortisone in a dose of 100 mg twice daily was shown to dramatically improve intensive care unit survival (90% vs. 12.5% for controls) (49). In a more recent study in catecholamine-dependent septic shock, hydrocortisone administered as a 100-mg intravenous bolus three times a day for at least 5 days (and then tapered over 6 days) was associated with a 31% absolute reduction in a 28-day mortality rate (45). Finally, a recently completed multicenter, placebo-controlled, randomized, double-blind study has evaluated the efficacy and tolerance of replacement therapy with a combination of hydrocortisone (50-mg intravenous bolus four times a day) and fludrocortisone (50 μg orally once a day) administered for 7 days. This study included 300 instances of catecholamine- and ventilator-dependent septic shock patients. The results of this study will be published in the near future.

In sum, a short course with high doses of corticosteroids should not be administered in severe sepsis, except for specific entities like severe typhoid fever (50), *Pneumocystis carinii* pneumonia in AIDS (51), or bacterial meningitis in children (52). However, the rationale for replacement therapy with hydrocortisone in catecholamine-dependent septic shock grows stronger.

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