Adjunctive Therapies in Severe Sepsis and Septic Shock: Current Place of Steroids

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For more than five decades, the use of corticosteroids as an adjunctive therapy to treat severe sepsis and septic shock has incited consistent debate. Negative results of the Corticosteroid Therapy of Septic Shock (CORTICUS) study evoked a revision of Surviving Sepsis Campaign guidelines suggesting a more restricted use of low-dose hydrocortisone only in patients with severe septic shock. Hemodynamic improvement by low-dose steroids was evident and independent from adrenal insufficiency, but did not improve survival. The roles of cortisol measurement and adrenal function tests for treatment decisions have been questioned. An international task force introduced the concept of critical illness–related corticosteroid insufficiency, which challenges the predominant role of adrenal dysfunction and underscores sustained inflammation due to tissue steroid resistance. Whether moderate steroid doses induce superinfections and muscle weakness is unclear. This article reviews recent publications, actual recommendations, ongoing discussions, and future perspectives.

Introduction

For more than five decades, no other adjunctive therapy has been more consistently debated than the use of corticosteroids for severe sepsis and septic shock. Consensus exists that a short course of high doses of glucocorticoids (up to 42 g hydrocortisone equivalent per day) is ineffective or harmful [1–3], and that a daily dose of hydrocortisone, 300 mg, should not be exceeded in patients with septic shock [4••,5••]. Application of low-dose corticosteroids for several days was found to improve shock reversal and survival [2,3] and was recommended as adjunctive therapy [6]. These recommendations were primarily based on results of an earlier French study, which showed a significant benefit on shock reversal and survival in patients who did not respond to corticotropin stimulation [7]. However, it remained controversial whether these results should be translated to all septic shock patients, and whether the indication for hydrocortisone application should depend on adrenal function testing. Another, more recent, investigation has since challenged previous study results and the clinical value of the corticotropin-stimulation test. This article reviews recent publications, actual recommendations, ongoing discussions, and future perspectives.

The Concept of Relative Adrenal Insufficiency

The rationale for hydrocortisone administration in septic shock is based on the concept of relative adrenal insufficiency (RAI), which implies an adrenal dysfunction with inadequate cortisol production for the severity of illness [8•]. It is assumed that, especially in septic shock, adrenal dysfunction plays the major role, although the entire hypothalamic-pituitary-adrenal (HPA) axis may be affected. Diagnosis of RAI was predominantly based on the measurement of random total cortisol or the delta increase of cortisol after stimulation with corticotropin, 250 μg. An increase of cortisol less than or equal to 9 μg/dL and/or random cortisol less than 15 μg/dL was regarded as a rationale for hydrocortisone therapy in studies and recommendations [7,8•,9,10•,11,12••]. The prevalence of RAI depends on the population and—most importantly—on diagnostic criteria, and thus varies from 0 to 77%. In a recent study, the prevalence of RAI was investigated with a metyrapone test in patients with severe sepsis and septic shock. RAI was diagnosed in 60% of patients, and a random cortisol less than 10 μg/dL and a delta cortisol less than 9 μg/dL had the best diagnostic accuracy [10•].

Controversy exists about appropriate cut-off values, limitations of delta cortisol to assess the entire HPA axis, relevance of measuring or calculating free biologic active cortisol, limitations of commercial assays (which may overestimate total cortisol in septic serum due to cross-reactivity with cortisol precursors), hourly variations of cortisol release with lost circadian rhythm (which questions the value of a single cortisol sample), or impact of protein binding on the interpretation of

Table 1. Comparison of baseline characteristics

Parameter	French trial [7]	CORTICUS [12••]
Time window, *h*	8	72
Fludrocortisone, *50 µg/d*	Yes	No
SAPS II score, *mean ± SD*	59 ± 21	49 ± 17
Mortality placebo group	61%	31%
Surgical patients	40%	67%
ACTH nonresponder	76%	47%
RRsyst < 90 mm Hg	> 1 h	Not required
Maximum vasopressor dose in placebo group, µg/kg/min, mean ± SD		
Norepinephrine	1.0 ± 1.1	0.4 ± 0.5
Dopamine	11.5 ± 5.7	7.9 ± 6.6
Epinephrine	1.0 ± 0.9	0.9 ± 2.6

ACTH—adrenocorticotropic hormone; CORTICUS—Corticosteroid Therapy of Septic Shock; RRsyst—systolic blood pressure; SAPS—Simplified Acute Physiology Score.

total cortisol measurements and on the release of free cortisol to the tissue [5••,8•,13•]. The discussion is even more complicated because the Corticosteroid Therapy of Septic Shock (CORTICUS) trial did not show that the hemodynamic effects of hydrocortisone depend on adrenal function (see below) [12••]. In view of the important question of HPA dysfunction in the critically ill, and uncertainty how, when, and in whom tests should be performed, the European Society of Intensive Care Medicine recently endorsed a consensus statement on the diagnosis and management of adrenal insufficiency in the critically ill (April 2008). Currently, routine random or delta cortisol measurements cannot be recommended to define patients with severe septic shock to receive hydrocortisone [4••,5••].

The CORTICUS Study

In the CORTICUS study, 251 patients with septic shock were randomized to receive hydrocortisone, 4 x 50 mg/d, for 5 days, followed by tapering until day 11, and 248 patients were randomized to receive placebo [12••]. RAI was diagnosed in 47% of patients at baseline. No significant difference was seen for 28-day mortality in all patients (hydrocortisone: 34.3%, placebo: 31.5%), nonresponders (hydrocortisone: 39.2%, placebo: 36.1%), or responders (hydrocortisone: 28.8%, placebo: 28.7%). The number of patients with reversed shock at day 28 was not significantly different in the whole group (hydrocortisone: 79.7%, placebo: 74.2%), nonresponders (76.0% vs 70.4%), or responders (84.7% vs 76.5%). However, the time until shock reversal was shorter for all patients who received hydrocortisone ($P < 0.001$), nonresponders ($P = 0.06$), and responders ($P < 0.001$). The median time until shock reversal was 3.3 days in the hydrocortisone group and 5.8 days in the placebo group (2.8 vs 5.8 days in responders, and 3.9 vs 6.0 days in nonresponders, respectively). Patients who received hydrocortisone had significantly more episodes of hyperglycemia (≥ 150 mg/dL; RR: 1.18 [1.07–1.31]), significantly more episodes of hypernatremia (≥ 150 mmol/L; RR: 1.58 [1.13–2.22]), and more superinfections (see below).

The results of the CORTICUS trial are in contrast to those of the French trial, which reported significant effects on survival and shock reversal in nonresponders who received hydrocortisone plus fludrocortisone for 7 days [7]. The current reading is that patients enrolled in the French trial were more severely ill, had higher Simplified Acute Physiology II scores, received more vasopressors, had more severe septic shock (systolic blood pressure < 90 mm Hg despite vasopressor and fluid therapy), more pneumonias, and there were more nonresponders (Table 1). This discrepancy of illness severity is also apparent by the twofold higher 28-day mortality in the placebo group of the French trial (61% vs 31%). The CORTICUS results may be similar to results of other experimental and clinical sepsis trials in which the treatment effect increased with the risk of death [14]. Interestingly, a post hoc analysis of patients in the CORTICUS study who had a systolic blood pressure that persisted below 90 mm Hg at day 1 showed a rate of death of 56.1% in the placebo group and an absolute reduction in mortality of 11.2% in the hydrocortisone group, which is similar to results of the French trial in the group of nonresponders (mortality 63%, reduction 10%) [7]. The CORTICUS results were recently addressed in a pneumonia model, in which mice were challenged with different doses of *Escherichia coli* and hydrocortisone combined with antibiotics. Irrespective of the hydrocortisone dose, survival was improved significantly; the efficacy of hydrocortisone therapy was independent from disease severity [15].

Table 2. Recommendations of the SSC 2008

	Grade
We suggest intravenous hydrocortisone be given only to adult septic shock patients after blood pressure is identified to be poorly responsive to fluid resuscitation and vasopressor therapy.	2C
We suggest the ACTH stimulation test not be used to identify the subset of adults with septic shock who should receive hydrocortisone.	2B
We suggest that patients with septic shock should not receive dexamethasone if hydrocortisone is available.	2B
We suggest the daily addition of oral fludrocortisone (50 μg) if hydrocortisone is not available and the steroid that is substituted has no significant mineralocorticoid activity. Fludrocortisone is considered optional if hydrocortisone is used.	2C
We suggest clinicians wean the patient from steroid therapy when vasopressors are no longer required.	2D
We recommend doses of corticosteroids comparable to > 300 mg hydrocortisone daily not be used in severe sepsis or septic shock for the purpose of treating septic shock.	1A
We recommend corticosteroids not be administered for the treatment of sepsis in the absence of shock. However, there is no contraindication to continuing maintenance steroid therapy or to using stress-dose steroids if the patient's endocrine or corticosteroid administration history warrants.	1D

ACTH—adrenocorticotropic hormone; SSC—Surviving Sepsis Campaign.
(*Data from* Dellinger et al. [4••].)

Other Recent Trials

A randomized study enrolled 29 patients with septic shock who received 0.2 mg/kg dexamethasone or placebo (3 times every 36 h) and reported significantly faster shock reversal, reduced 7-day mortality (67% vs 21%), and a trend toward reduction in 28-day mortality [16].

An open-label, randomized study investigated a 3-day therapy with methylprednisolone, 40 mg, in 31 patients with community-acquired pneumonia and reported shorter requirement for antibiotic use and faster resolution of clinical symptoms [17].

Surviving Sepsis Campaign Guidelines 2008

The results of the CORTICUS study had a major impact on the Surviving Sepsis Campaign (SSC) guidelines [4••] (Table 2). The revised guideline is based on the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system. The GRADE system includes a sequential assessment of quality of evidence, risk-benefit balance, burden and costs, and development and grading of recommendation. In the GRADE system, quality of evidence and strength of recommendation are separated. The quality of evidence is classified as high (grade A), moderate (B), low (C), or very low (D). Randomized trials begin as high, but may be downgraded due to study limitations. In contrast, observational studies begin as low, but may be upgraded on the basis of magnitudinal effect. The recommendations are classified as strong (grade 1) or weak (grade 2), and worded as "we recommend" and "we suggest," respectively. The grade of strong or weak is considered of greater clinical importance than a difference in the letter level of quality of evidence.

With regard to steroids, there was discussion whether a two-part recommendation should be given for two target populations or one for all patients with septic shock. The two-recommendation option suggested treating patients with hydrocortisone if blood pressure is inadequate with appropriate fluid resuscitation and vasopressor therapy, and not to treat if blood pressure is adequate with fluids and vasopressors, both graded as 2B.

An argument for the separate recommendation was that the French trial enrolled patients with severe shock within 8 hours, and the CORTICUS trial enrolled patients up to 72 hours without targeting patients unresponsive to vasopressors. Arguments for a single recommendation were the lack of a distinct blood pressure cut-off and standardization of fluid and vasopressor therapy to call the blood pressure unresponsive or poorly responsive. In a secret ballot of the SSC committee (31 vs 19, one abstention), the one-recommendation option was accepted.

International Task Force Recommendations

An international task force recommended describing HPA axis dysfunction in critical illness by the term *critical illness–related corticosteroid insufficiency* (CIRCI), and to avoid terms like absolute or relative adrenal insufficiency in this context [5••]. The concept of CIRCI extends the rationale for steroid therapy from impaired adrenal function/reserve to inadequate cellular corticosteroid activity in relation to the severity of the patient's illness. One principle of CIRCI is the insufficient glucocorticoid receptor–mediated down-regulation of proinflammatory transcriptions facts such as nuclear factor-κB, leading to persistent elevation of proinflammatory mediators. CIRCI may be caused not only by

decreased adrenal steroid production, but also by dysfunction at any point in the HPA axis, and/or by tissue resistance to steroids. CIRCI is recognized to be dynamic, that is, it may be not present at intensive care unit (ICU) admission but may develop and is usually reversible, unless structural damage of the adrenal gland is prominent.

CIRCI underscores the failure of activated glucocorticoid receptors to counterbalance the transcription of proinflammatory cytokines despite elevated levels of circulating cortisol—a condition defined as systemic inflammation-associated glucocorticoid resistance [18]. Tissue glucocorticoid resistance has been described in chronic inflammatory diseases such as chronic obstructive pulmonary disease, and evidence exists that tissue resistance also plays a major role in acute inflammation (eg, severe sepsis and acute respiratory distress syndrome [ARDS]). It is postulated that the glucocorticoid-resistant state may be reversed by quantitatively adequate and prolonged glucocorticoid supplementation [19]. Glucocorticoid resistance may be due to decreased glucocorticoid receptor number and affinity, increased expression of the β-glucocorticoid receptor isoform (unable to bind ligand), increased conversion of biologically active cortisol to inactive cortisone, and other factors [5••]. There is evidence that during systemic inflammation, mediators may stimulate or impair the synthesis and action of cortisol. For example, cortisol production may be sustained, despite decreased release of pituitary corticotropin, by immune mediators such as interleukin 6 [20]. Thus, the biologic cortisol activity may be time dependent and affected by illness severity, mediator production, cortisol resistance, and probably other unknown factors.

Recommendations for steroid therapy in septic shock are similar to those provided by the SSC. A grade 2B recommendation for moderate doses of methylprednisolone was given for early severe ARDS (PaO_2/FIO_2 < 200) and unresolving ARDS before day 14. The recommendation was based on data from 518 patients enrolled in five randomized trials. One study was in community-acquired pneumonia [21], one in early (< 3 days) ARDS [22••], two in late (> 7 days) ARDS [23••,24], and one was a post hoc analysis of patients with septic shock and ARDS enrolled in the French trial [25•]. There were differences regarding the steroid dose (hydrocortisone equivalent, 200–750 mg/d), treatment duration (7–32 days), steroid weaning (0–14 days), mode of application, study population, study design, and enrolled patients within and between studies limiting interpretation of the results [5••,26••].

However, all studies consistently reported significant effects on improvement of PaO_2/FIO_2 ratio, reduction of systemic inflammation, duration of mechanical ventilation, and length of ICU stay. When methylprednisolone was administered for more than 1 week, the mean difference of ventilator-free days was 5.59 (95% CI: 3.49–7.68; P < 0.001). When considering patients treated before day 14, the reduction of death was most pronounced in two small trials (n = 68) [21,24] (RR: 0.15, 0.04-0.59; P = 0.007), but was still significant in larger trials (n = 400) [22••,23••,25•] (RR: 0.78, 0.64-0.96; P = 0.02). Another meta-analysis concluded that current evidence does not support a role of corticosteroids in ARDS [27•]. A third meta-analysis addressed methodological limitations of the aforementioned meta-analyses [22••,27•], and suggested a possibility of reduced mortality and increased ventilator-free days in early ARDS [28••]. However, the two latter meta-analyses [27•,28••] included studies with high doses of steroids administered for a short course, and therefore probably underestimated the effect of dosage and duration of treatment.

Dose, Duration, and Tapering of Steroids

Recommendations for the optimal dose and duration of treatment with steroids are empiric. In patients with severe septic shock, hydrocortisone should be given in a dose of 200 mg/d in four divided doses or as a bolus of 100 mg followed by continuous infusion [4••,5••]. A randomized study compared a 3- versus 7-day application of hydrocortisone, 200 mg, in 82 patients with septic shock and RAI [11]. There was no significant difference in 28-day mortality, shock reversal, or mechanical ventilation; however, in patients with basal cortisol levels of less than 15 μg/dL or > 34 μg/dL, 28-day mortality was significantly lower (14.3% vs 50%, P = 0.022).

It was recommended that patients with severe septic shock should be treated for at least 7 days before tapering, assuming that there is no recurrence of signs of sepsis or shock [5••]. In most recent trials, the daily dose of hydrocortisone equivalent, 200 to 300 mg, was limited to a maximum of 5 to 7 days, eventually followed by dose tapering, and the cumulative dose rarely exceeded hydrocortisone, 1500 mg [7,12••,29]. In patients with early ARDS, methylprednisolone, 1 mg/kg per day, for at least 14 days, followed by a slow taper while monitoring indices of oxygenation was recommended [5••]. It is unknown whether prolonged application of hydrocortisone with low doses (eg, 50 mg) would be beneficial in severe septic shock to avoid recurrence of inflammation and adrenal dysfunction. The cumulative dose of steroids (> 1500 mg) was found to be a risk factor for prolonged mechanical ventilation [30•]. Evidence exists from patients with pneumonia that activation of the immune system may persist for weeks despite clinical improvement, and that ongoing inflammation is associated with poor hospital survival and 3 months' survival [31,32•]. Based on the concept of CIRCI, it may be tempting to extend the duration of therapy with a low dose of hydrocortisone in patients with septic shock, but no data exist to support this.

There is distinct evidence that rapid cessation of steroid therapy is associated with significant hemodynamic and immunologic rebound effects, shock reoccurrence, deterioration of oxygenation, and possibly steroid-induced

adrenal insufficiency [5••,26••,33,34]. There is no validated tapering protocol, but halving the dose every 2 to 3 days seems to be a practical approach. When the clinical situation deteriorates, reinstitution of hydrocortisone therapy should be considered [5••].

Bolus Versus Continuous Steroid Application

Intensive insulin therapy (IIT) to achieve euglycemia has a significant impact on morbidity and mortality, especially in patients with prolonged ICU stay [35,36••]. A risk-benefit discussion is needed on targeting euglycemia in patients with severe sepsis. In the Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) study, mean blood glucose was lower in the IIT group (112 mg/dL vs 151 mg/dL, $P < 0.001$), but there were no significant differences with regard to 28-day mortality or morbidity [37••]. IIT patients had significantly more hypoglycemic (glucose ≤ 40 mg/dL) episodes (17.0% vs 4.1%, $P < 0.001$), similar to the rate observed in medical ICU patients [36••]. A before-and-after IIT implementation study with glucose target values of less than 140 mg/dL reported an absolute mortality reduction of 27% in 53 patients with septic shock; hypoglycemia was not a problem [38]. Two observational studies suggested that the target value for improved outcome is between 145 and 180 mg/dL [39,40]. In view of the observed reduction of morbidity and mortality with IIT at one trial site, and safety concerns and unclear efficacy in patients with severe sepsis at the other site, the SSC suggests maintaining glucose levels less than 150 mg/dL (grade 2C) [4••].

An important aspect may be the mode of steroid application. In a retrospective analysis from a cohort of 7049 critically ill patients, mean blood glucose and glucose variability in the range of 30 to 40 mg/dL were significant independent predictors of ICU and hospital mortality [41•]. A meta-analysis did not demonstrate a risk of hyperglycemia in septic shock patients treated with steroids [42]. However, definitions of hyperglycemia in these studies were different from those currently recommended (< 150 mg/dL), probably underestimating the effects of low-dose steroids. Repeated bolus application of hydrocortisone, 50 mg, led to undulation of cortisol, with peak values of 150 to 200 μg/dL and nadir values of 40 to 50 μg/dL [13•]. A randomized study compared a bolus and continuous regimen in 48 patients with septic shock [43•]. Blood glucose was titrated to levels of 72 to 126 mg/dL (4–7 mmol/L). In the bolus group, staff workload increased significantly due to more frequent necessary insulin adjustments to maintain the target value, and significantly more hyperglycemia (> 126 mg/dL) occurred; however, values greater than 150 mg/dL were rare. So, why worry about the mode of application? We observed stable blood glucose of about 130 mg/dL during continuous infusion of hydrocortisone, but marked interindividual variation and increases to levels above 150 mg/dL after an intermittent bolus of hydrocortisone, 50 mg [44•]. One might assume that a mean glucose value of 130 mg/dL is probably closer to current routine practice. Indeed, in the CORTICUS trial, significantly more episodes of hyperglycemia greater than 150 mg/dL were observed during repeated bolus application of hydrocortisone than in the placebo group. Thus, a continuous infusion may be preferable to reduce frequent insulin adjustments, staff workload, and hyperglycemic episodes.

Shock Reversal and Mortality

Although the CORTICUS study did not show a significant effect on shock reversal on day 28, the data are consistent with results of other trials showing that moderate doses of steroids accelerate hemodynamic stabilization. A meta-analysis on six studies with a total of 952 patients revealed a relative risk for shock reversal on day 7 of 1.39 (95% CI: 1.24–1.55; $P < 0.00001$) [5••]. By combining current data, shock reversal is independent from adrenal function [3,5••,12••]. One could argue that the applied hydrocortisone dose is pharmacologic and not substituting or replacing a physiologic hydrocortisone deficit. Hydrocortisone inhibits inducible nitric oxide production, which may contribute to shock reversal [33]. Preliminary data from a CORTICUS substudy indicate that hydrocortisone-induced nitric oxide suppression is independent from adrenal function, as were the effects of hydrocortisone on numerous other protein and genomic parameters (DNA microarray) [45].

However, faster shock reversal was not associated with improved mortality in CORTICUS [12••]. As outlined above, hydrocortisone therapy is probably most effective in severe cases. It was also suggested that an increased number of side effects counterbalanced hemodynamic improvement. One might also speculate that hydrocortisone therapy might be more effective when initiated earlier, probably even before shock occurrence (see below).

Overall, risk reduction for 28-day mortality has lost significance in 965 patients with septic shock from six trials (RR: 0.92; 0.79–1.06; $P = 0.25$) [5••]. In contrast, when recognizing 1230 patients from 12 trials with severe sepsis or septic shock, low-dose steroids still have a significant effect on 28-day mortality (RR: 0.86; 0.75–0.98; $P = 0.02$) (Personal communication, D. Annane).

Side Effects of Steroids

An increased number of superinfections, including new sepsis and septic shock, were reported in CORTICUS (hydrocortisone: 78/234 [33%], placebo: 61/232, [26%]; RR: 1.27 [0.96–1.68]). This is in contrast to other trials, which reported no difference or a decreased incidence of superinfections in septic shock [7,42], or early and late ARDS [22••,23••,28••], but a decreased development of septic shock in community-acquired pneumonia [21] and late ARDS [23••]. The main

difference in superinfection subgroups was the development of new septic shock (hydrocortisone: 14/234 [6%], placebo: 5/232, [2%]; RR: 2.78 [1.02–7.58]); however, it is uncertain how many of these events were due to rebound inflammation after hydrocortisone cessation and shock reversal, or caused by new pathogens. Preliminary data from the CORTICUS substudy on immune responses do not support hydrocortisone-induced immunosuppression, which concurs with other reports [29,33]. For example, there was no significant difference with regard to HLA-DR receptor expression on monocytes, T-helper cell numbers, and T-helper-2 proliferation, but anti-inflammatory interleukin 10 was significantly reduced. However, when steroids are administered for a prolonged period, infection surveillance is recommended, because steroids dampen signs of systemic inflammation (eg, fever and C-reactive protein) [5••].

In another study, a 15-fold increased risk was reported for development of muscle weakness in critically ill patients treated with steroids [46]. In this study, 9 of 26 patients who received steroids probably (although it was not reported) received low-dose hydrocortisone for septic shock and the remaining higher doses for other indications (eg, lymphomas). High-dose glucocorticoids, especially in combination with muscle relaxants, are recognized as important risk factors, but there is also increasing evidence that systemic inflammation is the main trigger for development of critical illness polyneuromyopathy [47••]. One might speculate that early inhibition of inflammation by moderate doses of steroids is even protective. Indeed, moderate doses of steroids were found to accelerate weaning in patients with ARDS [23••], and were protective for development of critical illness polyneuromyopathy in combination with glucose control [30•]. In a prospective randomized trial (n = 93), mechanically ventilated patients with RAI could be weaned more rapidly when low-dose hydrocortisone was administered (hydrocortisone: 91.4%, placebo: 68.6%, P = 0.035) [48•].

It should be noted that the SSC regarded both superinfection and muscle weakness as strong arguments for restricted use of steroids in patients with septic shock [4••].

Fludrocortisone

The additional daily oral dose of fludrocortisone, 50 μg, is considered optional [4••,5••]. A dose of hydrocortisone, 50 to 100 mg, is sufficient to cover mineralocorticoid deficiency in adrenal crisis of Addison disease [8]. It is uncertain whether the situation is different in septic shock, and whether the different results of CORTICUS and the French trial were due to the additional dose of fludrocortisone. The question is currently under investigation in two randomized trials (ClinicalTrials.gov identifiers: NCT 00368381, NCT 00320099).

Low-Dose Hydrocortisone in Severe Sepsis

Based on the current data, hydrocortisone treatment cannot be recommended in patients with severe sepsis without shock [4••]. It is well recognized that development of shock increases the risk of death by 70% [49], but there is currently no established therapy to prevent shock. High-dose steroids failed to prevent progression to shock in patients with severe sepsis, but the dose was probably too high and the application too short [50]. Indeed, in patients with community-acquired pneumonia, prolonged hydrocortisone infusion significantly prevented shock development (0% vs 46%, $P < 0.0001$) and was associated with substantial reduction of morbidity and mortality [21]. Are we probably too late with low-dose hydrocortisone therapy, and can these encouraging results be translated to a broader spectrum of patients? This challenging question will be addressed in the Hydrocortisone for Prevention of Septic Shock (HYPRESS) study (ClinicalTrials.gov identifier: NCT 00670254).

Conclusions

Administration of low-dose hydrocortisone is suggested only in patients with septic shock who are poorly responsive to fluids and vasopressors. Hemodynamic stabilization is independent from adrenal function and random or stimulated cortisol measurements should not be taken routinely for deciding on a treatment. The concept of CIRCI questions the notion of predominant adrenal dysfunction and underscores tissue steroid resistance, which may be overcome by prolonged administration of moderate doses of steroids; however, further trials are needed for confirmation. Ongoing trials address the role of fludrocortisone and shock prevention by steroids.

Disclosures

No potential conflicts of interest relevant to this article were reported.

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