

## Adrenal function in sepsis and septic shock

Cristiane Freitas Pizarro,<sup>1</sup> Eduardo Juan Troster<sup>2</sup>

### Abstract

**Objective:** To review diagnostic criteria and treatment of adrenal insufficiency in pediatric patients with severe sepsis and septic shock.

**Sources:** Articles were selected using MEDLINE (1966-June 2007), Embase (1994-2007) and Cochrane Library (2000-2007) databases. following key words were utilized: septic shock, sepsis, corticosteroids, adrenal insufficiency and children.

**Summary of the findings:** There are no well established and accepted criteria to define adrenal insufficiency in critically ill patients. Incidence of adrenal insufficiency varies according to different criteria, and it may range between low values of 15% and high values of 61%. The rapid corticotropin stimulation test is widely used as a method to identify adrenocortical hyporesponsiveness, but controversy exists as to the corticotropin dose to be used. The 250 µg dose is the standard dose. Low doses of corticotropin (1 µg) have recently been proposed, suggesting that they may have higher sensitivity. There are still doubts as to the efficacy of low doses of corticosteroids in children with catecholamine-refractory shock. Further studies are needed to determine whether the treatment of these patients would change morbidity and/or mortality.

**Conclusion:** Adrenal insufficiency is common in children with severe sepsis and septic shock and may contribute to the development of catecholamine-refractory shock. However, doubts still persist regarding the efficacy of replacement therapy with low-doses steroids.

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### Introduction

Despite the advances in intensive care units (ICU), septic shock and severe sepsis remain a major cause of morbidity and mortality. In fact, incidence of septic shock and severe sepsis has been increasing over the past 30-40 years. It is estimated that in the USA there are about 750,000 new cases of severe sepsis every year.<sup>1,2</sup> Therefore, there is a clear growing concern about the development of therapeutic strategies that contribute to reduction in morbidity and mortality rates; among them, administration of corticosteroids has once again come under discussion.

In the 1970's and 1980's many studies were carried out with the aim of showing the therapeutic effects of corticosteroids in patients with severe sepsis and septic shock. Most of these studies used high doses of corticosteroids for a short period of time. However, in 1995 two meta-analyses were

published and did not show satisfactory results concerning survival.<sup>3,4</sup> New studies have currently shown good results as to survival by using low doses of hydrocortisone that are offered for a longer period of time (at least 3 days), especially in the group of patients with relative adrenal insufficiency and catecholamine-refractory shock.<sup>5-7</sup>

Many studies have recently assessed the function of the adrenal gland in patients with severe sepsis and septic shock, as an attempt to establish the relationship of an adrenal response that is considered inadequate for the stress situation with intensity of hemodynamic changes. Such studies have found a high incidence of inadequate adrenal function and a strong association with catecholamine refractory shock.<sup>8-11</sup>

However, many questions still have to be explained regarding presence of adrenal insufficiency in sepsis and septic shock.

1. Mestre em Pediatria, Faculdade de Medicina, Universidade de São Paulo (USP), São Paulo, SP, Brazil. Coordenadora da Pediatria, Unidade de Terapia Intensiva Pediátrica, Hospital Estadual Vila Alpina, São Paulo, SP, Brazil.
2. Unidade de Terapia Intensiva Pediátrica, Departamento de Pediatria, Instituto da Criança, Faculdade de Medicina, Universidade de São Paulo, SP, Brazil.

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- a) What is the incidence of adrenal insufficiency in patients with severe sepsis and septic shock?
- b) What is the appropriate level of baseline cortisol after the rapid corticotropin (ACTH) stimulation test in patients with severe sepsis and septic shock?
- c) What is the ideal treatment for patients with septic shock and adrenal insufficiency?

Based on those questions, we felt encouraged to perform this study to review diagnostic criteria and treatment of adrenal insufficiency in pediatric patients with severe sepsis and septic shock.

### Regulation of glucocorticoid secretion

Glucocorticoids are 12-carbon molecules derived from cholesterol and are produced by the adrenals in response to ACTH. They are produced continuously and are influenced by circadian rhythm - have higher levels in the morning and lower levels at night. However, in a stress situation, such rhythm is lost.

During inflammatory processes, inflammatory cytokines, such as interleukin-1 (IL-1), tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) and interleukin-6 (IL-6), favor release of corticotrophin-releasing factor (CRF) and arginine vasopressin (AVP) by the hypothalamus. Then, CRF enhances the production of ACTH by the anterior pituitary gland. When ACTH enters the systemic circulation, it activates the adrenal cortex, activating production of glucocorticoids and other steroids. Glucocorticoids, through a feedback mechanism, inhibit the hypothalamic-pituitary-adrenal axis.<sup>12,13</sup>

### Hypothalamic-pituitary-adrenal axis in septic shock

It has been well described in the literature that, under stress situations, such as severe sepsis and septic shock, there is a stimulation of the hypothalamic-pituitary-adrenal axis and, therefore, an increase in cortisol secretion and loss of circadian rhythm. Activation of the hypothalamic-pituitary-adrenal axis is a crucial component of the patient's adaptation to a stress situation and contributes to maintenance of homeostasis. In ICU the higher the scores of disease severity, the higher the expected cortisol levels and mortality rates.<sup>13</sup>

Relative adrenal insufficiency is present when adrenal response is inadequate for the stress situation. These patients usually have the highest levels of baseline cortisol, but do not respond to the ACTH stimulation test, i.e., do not have adrenal reserve.<sup>8,14</sup>

On the other hand, absolute adrenal insufficiency is characterized by low levels of baseline cortisol and by non-response to the ACTH stimulation test. Such response pattern in patients with septic shock is not what we often observe,

since in that situation activation of the hypothalamic-pituitary-adrenal axis is expected.<sup>8,14</sup>

### Causes of adrenal insufficiency

The cause of adrenal insufficiency in patients with severe sepsis and septic shock is multifactorial. Therefore, a primary adrenal insufficiency can be a result of destruction of the adrenal gland: by either direct or indirect action of infectious agents, due to hemorrhage - coagulation disorder (for example: Waterhouse-Friderichsen syndrome); or induced by drugs, such as etomidate and ketoconazole. However, it usually occurs as secondary adrenal insufficiency (disorder at a hypothalamic-pituitary integrity) as a consequence of reduction in CRF release, inhibited by cytokines and other mediators of inflammatory response released during sepsis. Chronic use of glucocorticoids can also be associated with suppression of the hypothalamic-pituitary-adrenal axis, as well as presence of a preexisting disease at hypothalamus, pituitary or adrenal level.<sup>13,15</sup>

Adrenal insufficiency can also be a result of reduction in number of glucocorticoid receptors or reduction in its affinity by the receptor, which leads to increased peripheral resistance to glucocorticoids.<sup>13</sup>

### Clinical manifestations of adrenal insufficiency

Acute adrenal insufficiency can be clinically indistinguishable from septic and hypovolemic shock, being a differential diagnosis.

There are many symptoms associated with adrenal insufficiency. Diagnosis is often suspected when these patients have hypotension refractory to fluid therapy and to vasoactive drugs. Other symptoms related to adrenal insufficiency are abdominal pain, fever in the presence of negative cultures and non-responsive to antibiotics, inexplicable changes in consciousness level, electrolytic abnormalities (hypoglycemia, hyponatremia, hyperkalemia), neutropenia and eosinophilia.<sup>15-17</sup>

### Incidence of adrenal insufficiency

Incidence of adrenal insufficiency ranges according to population and criteria used to define this condition.<sup>5,8,9,13,17-26</sup>

Adequate level of cortisol after the ACTH stimulation test for critically ill patients is still a controversial issue in the literature.<sup>5,13,17,21,27-31</sup> It is known that under stress situations, such as infection, trauma, burn, pain, hypotension, hemorrhage, hypovolemia, tissue lesion, among many others, there is a stimulation of the hypothalamic-pituitary-adrenal axis and, thus, an increase in cortisol secretion and loss of circadian rhythm.<sup>10,13</sup> For example, during a surgical procedure, cortisol increases in the immediate post-operative period, reaching levels between 30-45  $\mu\text{g/dL}$ , and returns to

basal levels in approximately 72 hours. In critically ill patients, the tendency is for cortisol to increase even more.<sup>13</sup>

In ICU the higher the scores of disease severity, the higher the cortisol levels and mortality rates. Schein et al. studied the concentration of plasma cortisol in 37 patients with septic shock and observed that it was increased (mean 50.7 µg/dL) when compared with normal patients (mean 10-20 µg/dL).<sup>29</sup> Bone et al. assessed 65 children with meningococcal disease and found mean cortisol value of 41.5 µg/dL at admission.<sup>32</sup> Rivers et al. assessed adrenal function in 104 patients submitted to surgery and who needed vasopressors, and found mean baseline cortisol of 29.9 µg/dL.<sup>22</sup> The main controversy in the literature has been the definition of which cortisol value represents an adequate adrenal response to stress and below which value should be considered as adrenal insufficiency.

Classical studies consider levels between 18-20 µg/dL<sup>19,33,34</sup> as adequate for the stress situation. Marik & Zaloga, in their studies, considered cortisol values higher than 25 µg/dL<sup>13</sup> as the most appropriate for the stress situation. Annane et al., in their study, showed the importance of performing the ACTH stimulation test to detect adrenal dysfunction and consider that not increment < 9 µg/dL would lead to the diagnosis of relative adrenal insufficiency.<sup>9</sup> Cooper & Stewart suggest the following values for diagnosing adrenal insufficiency: baseline cortisol < 15 µg/dL or presence of basal cortisol between 15-34 µg/dL, with an increment < 9 µg/dL after the ACTH stimulation test.<sup>17</sup>

For the pediatric age group, there are few studies concerning cortisol level in stress situations. In a study carried out by Hatherill et al., a cortisol increment was used to diagnose adrenal insufficiency after the ACTH stimulation test ≤ 7.5 µg/dL.<sup>20</sup> In a study performed by Menon & Clarson, baseline cortisol level < 7 µg/dL was considered with peak < 18 µg/dL.<sup>24</sup> In a

study performed by our group, at Instituto da Criança, published in 2005, presence of a cortisol increment ≤ 9 µg/dL after the ACTH stimulation test was used as a criterion to define inadequate adrenal response, with the aim of detecting not only patients with absolute adrenal insufficiency, but especially those with relative adrenal insufficiency. In that study, the patients with inadequate adrenal response were divided into two groups: 1) absolute adrenal insufficiency – baseline cortisol < 20 µg/dL and increment ≤ 9 µg/dL after the ACTH stimulation test; 2) relative adrenal insufficiency – patients with baseline cortisol ≥ 20 µg/dL and increment ≤ 9 µg/dL.<sup>8,14</sup>

Therefore, incidence of adrenal insufficiency may range between 15-61%, according to the criteria are used.<sup>8,9,18-22,24,25,35,36</sup> Table 1 shows the incidence of adrenal insufficiency in critically ill patients the according to various published definitions.

### Tests to evaluate adrenal function

The following methods can be used to evaluate the hypothalamic-pituitary-adrenal axis under stress situations:<sup>15,28</sup>

#### Dosage of basal cortisol (at random)

Cortisol dosage, without a defined schedule, is performed in patients under stress situations, since the circadian cycle is lost.

#### Insulin tolerance test (ITT)

It is considered gold standard to diagnose adrenal insufficiency when assessing axis integrity; however, it is not feasible under stress situations due to risk of hypoglycemia.

#### Metyrapone test

The metyrapone test was developed by Liddle et al.<sup>28</sup> to evaluate pituitary reserve. Metyrapone inhibits enzyme P450

**Table 1** - Incidence of adrenal insufficiency in critically ill patients according to various published definitions

Author (year)	Population	Cortisol level (µg/dL)	Incidence
Rothwell et al. <sup>21</sup> (1991)	Adults	Cortisol increment < 9 after ACTH stimulation test	40%
Soni et al. <sup>19</sup> (1995)	Adults	Cortisol < 18 after ACTH stimulation test	24%
Hatherill et al. <sup>20</sup> (1999)	Pediatric	Cortisol increment < 7.5 after ACTH stimulation test	52%
Loisa et al. <sup>25</sup> (2002)	Adults	Baseline cortisol < 25 and increment ≤ 9 after ACTH stimulation test	15%
Bone et al. <sup>32</sup> (2002)	Pediatric	Baseline cortisol < 5 or cortisol < 18 after ACTH stimulation test	17%
Menon & Clarson <sup>24</sup> (2002)	Pediatric	Baseline cortisol < 7 or cortisol < 18 after ACTH stimulation test	31%
Marik & Zaloga <sup>36</sup> (2003)	Adults	Baseline cortisol < 25	61%
Pizarro et al. <sup>8</sup> (2005)	Pediatric	Cortisol increment ≤ 9 after ACTH stimulation test	44%

ACTH = adrenocorticotrophic hormone.

C11, which converts 11-deoxycortisol (compound S) into cortisol, consequently reducing serum levels of cortisol and increasing 11-deoxycortisol levels. Reduction in serum cortisol stimulates release of ACTH by feedback, acting at a hypothalamic-pituitary level. Adequate adrenal production occurs when compound S is higher than 7.0 µg/dL, independent of cortisol value. Required waiting time for its execution is at least 8 hours between administration of metyrapone and serum dosages, and the possibility of this test being affected by use of other drugs (glucocorticoids, phenytoin and phenobarbital), as well as the very reduction of serum cortisol determined by the test, determines its lack of usefulness in severe patients.

### **ACTH stimulation test**

It is performed to evaluate adrenal gland response and reserve, i.e., it is important to detect relative adrenal insufficiency. The literature is controversial as to which corticotropin dose should be used to perform the ACTH stimulation test. Traditionally, a dose of 250 µg ACTH (supraphysiological dose) is used. However, nowadays lower doses have been successfully used (0.5-2 µg ACTH), since they have better sensitivity when compared with supraphysiological doses.<sup>8,10,14,37,38</sup> Nevertheless, a recent meta-analysis performed in adults, comparing tests using high doses (250 µg) and low doses (1 µg) of corticotropin, failed to show a test superiority when low doses were used.<sup>39</sup> Therefore, this issue is still being discussed in the literature (Table 2).

The ACTH stimulation test was chosen to evaluate adrenal function because it is a simple and fast procedure. Other tests, although having more reliable results, are more difficult to perform, and most of them are contraindicated in critically ill patients.

We must mention another issue concerning the identification of adrenal insufficiency: free cortisol vs. baseline cortisol. It is known that 90% of circulating cortisol in human serum is bound to proteins - corticosteroid-binding-globulin and albumin (CGB). Thus, it is expected that, in the presence of a

reduction in levels of transport proteins (for example, albumin), concentration of total serum cortisol is altered, affecting interpretation of tests used to evaluate adrenal function. For example, a study carried out by Hamrahian et al. showed that 40% of critically ill patients with hypoalbuminemia had a reduction in total cortisol levels.<sup>40</sup> Therefore, studies performed in adult patients have suggested that, in the presence of significant hypoproteinemia (albumin levels lower than 2.5 g/dL), free serum cortisol should be dosed before starting supplementation with corticosteroids.<sup>37,40</sup>

### **Clinical consequences of adrenal insufficiency**

Studies have recently demonstrated an association between adrenal insufficiency, catecholamine refractory shock and mortality.<sup>8,11,37,41</sup> A study conducted by our group showed that patients with adrenal insufficiency (absolute and relative) usually progress with catecholamine-refractory shock (100 and 80%, respectively) and may be benefited from corticosteroid therapy. In that study, increased mortality was also seen in the group of patients with inadequate adrenal response.<sup>8,14,37</sup>

### **Corticosteroid therapy in septic shock**

Since their discovery, corticosteroids have received a wide range of clinical indications, mainly because they are one of the most powerful anti-inflammatory drugs known to date. In 1940, Perla & Marmorston and, in 1951, Hahn et al. were the first authors to publish studies suggesting corticosteroid therapy for critically ill patients (pneumonia, bacteremia and generalized infection).<sup>41,42</sup> However, their use is still quite controversial in the literature.<sup>43-46</sup>

In the 1970's and 1980's many studies were carried out with the aim of showing the therapeutic effects of corticosteroids in patients with severe sepsis and septic shock. Most of these studies used high doses of corticosteroids (dexamethasone or methylprednisolone) for a short period of time.<sup>47-56</sup> Nevertheless, two meta-analyses published by Lefering et al. and Cronin et al. in 1995 did not show satisfactory results concerning survival<sup>3,4</sup> (Table 3).

**Table 2** - Synthetic ACTH dose used in different studies in the pediatric age group

<b>Author (year)</b>	<b>ACTH dose used in the stimulation test</b>	<b>Definition of adrenal insufficiency</b>
Hatherril et al. <sup>20</sup> (1999)	145 µg/m <sup>2</sup> (max. 250 µg)	Cortisol increment < 7.5µg/dL after ACTH stimulation test
Bone et al. <sup>32</sup> (2002)	0.5 µg/m <sup>2</sup>	Baseline cortisol < 5µg/dL or cortisol < 18µg/dL after ACTH stimulation test
Menon & Clarson <sup>24</sup> (2003)	< 10 kg: 125 µg > 10 kg: 250 µg	Baseline cortisol < 7µg/dL or cortisol < 18µg/dL after ACTH stimulation test
Pizarro et al. <sup>8</sup> (2005)	250 µg	Cortisol increment ≤ 9µg/dL after ACTH stimulation test

ACTH = adrenocorticotrophic hormone.

**Table 3** - Summary of publications included in two meta-analyses: Cronin et al. (1995) and Lefering et al. (1995), with regard to type of corticosteroid used, dose and duration of treatment for critically ill patients

Author (year)	n	Drug	Dose (duration)
Luce et al. <sup>47</sup> (1988)	75	M	30 mg/kg 4 times (24 h)
Veterans Administration <sup>48</sup> (1987)	223	M	30 mg/kg bolus followed by 5 mg/kg/h (9 h)
Bone et al. <sup>49</sup> (1987)	381	M	30 mg/kg (24 h)
Sprung et al. <sup>50</sup> (1984)	59	M, D	30 mg/kg, 6 mg/kg (repeat after 4 h if necessary)
Thompson et al. <sup>51</sup> (1976)	60	M	30 mg/kg one time
Lucas et al. <sup>52</sup> (1984)	48	D	2 mg/Kg, 6 mg/kg in continuous infusion (48 h)
Schumer et al. <sup>53</sup> (1976)	172	M, D	30 mg/kg, 3 mg/kg (repeat once after 4 h if necessary)
Klastersky et al. <sup>54</sup> (1971)	85	B	1 mg/kg/day (3 days)
Cooperative Study Group <sup>55</sup> (1963)	194	H	300 mg followed by 50 mg/day (5 days)
Bennet et al. <sup>57</sup> (1963)	194	H	300 mg followed by 50 mg/day (6 days)

B = betamethasone; D = dexamethasone; H = hydrocortisone; M = methylprednisolone.

In contrast, recent studies have demonstrated good outcomes as to survival by using low hydrocortisone doses (200-300 mg/day), offered by a longer period of time (at least 3 days)<sup>5,57-61</sup> (Table 4).

Those studies also demonstrated better progress when corticosteroid therapy was used in the group of patients who

had catecholamine-refractory shock.<sup>5,46,57,50,60,61</sup> In addition, they elected hydrocortisone as the choice corticosteroid, since it has a mineralocorticoid activity, whereas methylprednisolone and dexametasones do not have such activity. They also demonstrated that 20 mg of hydrocortisone are equivalent to 0.05 mg of fludrocortisone, and 0,05-2mg of fludrocortisone are recommended as mineralocorticoid

**Table 4** - Recent studies on corticosteroid therapy: type of corticosteroid to be used, dose and duration of treatment

Author (year)	Type of study	n	Drug	Dose (duration)
Bollaert et al. <sup>58</sup> (1998)	Randomized Double-blind Controlled Multi-center	41	H	100 mg EV for 5 days, then reduce the dose in half every 3 days.
Briegel et al. <sup>59</sup> (1999)	Randomized Double-blind Controlled	40	H	100 mg EV followed by 0.18 mg/kg/h until shock reversion, then reduce 0.08 mg/kg/h in 6 days until dose of 24 mg/day.
Chawla et al. <sup>61</sup> (1999)	Randomized Double-blind Controlled	44	H	100 mg EV 8/8 h for 3 days.
Annane et al. <sup>5</sup> (2002)	Randomized Double-blind Controlled Multi-center	299	H	50 mg EV every 6 h for 7 days associated with 9- $\alpha$ -fludrocortisone 50 $\mu$ g/day
Keh et al. <sup>60</sup> (2003)	Randomized Double-blind Controlled	40	H	100 mg EV in 30 min followed by 10 mg/h for 3 days
Oppert et al. <sup>62</sup> (2005)	Randomized Double-blind Controlled	41	H	50 mg EV followed by 0.18 mg/kg/h until shock reversion, 0.06 mg/kg/h for 24 h, then reduce 0.02 mg/kg/h every day

EV = endovenous; H = hydrocortisone.

replacement in adrenal insufficiency.<sup>6</sup> Those data were confirmed in 2004 by a meta-analysis published by Annane et al. and a review article published by Keh & Sprung.<sup>6,7</sup>

With regard to the pediatric age group, there are few studies on corticosteroid therapy in patients with septic shock. So far, there has been no consensus in the literature regarding hydrocortisone dose to be used, form of administration (bolus or continuous), duration of treatment, need of weaning and at which shock stage it should be prescribed.

In 2002, the American College of Critical Care Medicine (ACCM) developed new guidelines and parameters of clinical practice for hemodynamic support in newborns and children with septic shock, with the aim of improving evolution of these patients. The members of that committee verified that adrenal insufficiency was more frequent than what had been assumed and that hydrocortisone replacement could save the life of these children. Based on that fact, they suggested hydrocortisone therapy for all children who had any risk factor for adrenal insufficiency and for those who developed catecholamine-refractory shock. Risk patients were considered: children with purpura fulminans, children with pituitary or adrenal abnormalities and children who have previously received steroid therapies for chronic illness. The dose recommended by that committee ranged between 1-2 mg/Kg (stress dose) and 50 mg/kg (shock dose) in bolus, followed by a dose of 2 mg/kg/hour in continuous infusion for 24 hours.<sup>62</sup> Such doses were based on two studies performed in children with shock secondary to dengue.<sup>63,64</sup> Such doses are currently considered too high.

In 2005, Hildebrandt et al. conducted a literature review with the aim of evaluating clinical practice as to use of corticosteroids in septic shock in 25 pediatric ICU in the UK. They verified that routine corticosteroids were used in 76% of the ICU, but only one ICU had a protocol. In 84% of them, corticosteroids were used in the presence of persistent hypotension, despite using vasoactive drugs, and the drug of choice was hydrocortisone in 79% of cases.<sup>65</sup>

Therefore, new multi-center and randomized clinical trials are needed, so that true guidelines can be developed concerning corticosteroid therapy in patients with septic shock with suspicion of adrenal insufficiency. Our suggestion now is to use low doses of hydrocortisone (10 mg/kg in bolus, followed by 100 mg/m<sup>2</sup>/day every 6 hours) as soon as catecholamine-refractory shock is detected for 5 days or until vasoactive drugs are discontinued. As to baseline cortisol dosage and ACTH stimulation test, we suggest performing it whenever possible in all children with catecholamine-refractory shock, with the aim of guiding the therapy, and not starting it.

## Conclusion

Adrenal insufficiency is common and underdiagnosed in children with severe sepsis and septic shock. We believe that,

in the presence of catecholamine-refractory shock, the ACTH stimulation test has an important prognostic value, helping identify patients with relative adrenal insufficiency and serving as a therapeutic guide.

There are still doubts as to the therapy. New multi-center and randomized clinical trials are needed to determine whether the therapy using low doses of hydrocortisone will contribute to reducing morbidity and mortality rates without a significant increase in adverse events.

## References

1. Sessler CN, Shepherd W. New concepts in sepsis. *Curr Opin Crit Care*. 2002;8:465-72.
2. Angus DC, Wax RS. Epidemiology of sepsis: an update. *Crit Care Med*. 2001;29:S109-16.
3. Cronin L, Cook DJ, Carlet J, Heyland DK, King D, Lansang MA, et al. Corticosteroids treatment for sepsis: a critical appraisal and meta-analysis of the literature. *Crit Care Med*. 1995;23:1430-9.
4. Lefering R, Neugebauer EA. Steroid controversy in sepsis and septic shock: a meta-analysis. *Crit Care Med*. 1995;23:1294-303.
5. Annane D, Sébille V, Charpentier C, Bollaert PE, François B, Korach JM, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA*. 2002;288:862-71.
6. Keh D, Sprung CL. Use of corticosteroid therapy in patients with sepsis and septic shock: an evidence-based review. *Crit Care Med*. 2004;32:S527-33.
7. Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y. Corticosteroids for severe sepsis and septic shock: a systematic review and meta-analysis. *BMJ*. 2004;329:480-9.
8. Pizarro CF, Troster EJ, Damiani D, Carcillo JA. Absolute and relative adrenal insufficiency in children with septic shock. *Crit Care Med*. 2005;33:855-9.
9. Annane D, Sébille V, Troché G, Raphael JC, Gajdos P, Bellissant E. A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. *JAMA*. 2000;28:1038-44.
10. Casartelli CH, Garcia PCR, Piva JP, Branco RG. Insuficiência adrenal na criança com choque séptico. *J Pediatr (Rio J)*. 2003;79:S169-76.
11. de Jong MF, Beishuizen A, Spijkstra JJ, Groeneveld ABJ. Relative adrenal insufficiency as a predictor of disease severity, mortality, and beneficial effects of corticosteroid treatment in septic shock. *Crit Care Med*. 2007;35:1-8.
12. Annane D, Cavallion JM. Corticosteroids in sepsis: from bench to bedside? *Shock*. 2003;20:197-207.
13. Marik PE, Zaloga GP. Adrenal insufficiency in the critically ill: a new look at an old problem. *Chest*. 2002;122:1784-96.
14. Pizarro CF. Insuficiência adrenal absoluta e relativa em crianças com sepse grave e choque séptico [dissertação]. São Paulo: Faculdade de Medicina da Universidade de São Paulo; 2004.
15. Marik PE, Zaloga GP. Hypothalamic-pituitary-adrenal insufficiency. *Crit Care Clin*. 2001;17:25-38.
16. Lamberts SW, Bruining HA, de Jong FH. Corticosteroid therapy in severe illness. *N Engl J Med*. 1997;337:1285-92.

17. Cooper MS, Stewart PM. Corticosteroids insufficiency in acutely ill patients. *N Engl J Med.* 2003;348:727-34.
18. Bouachour G, Tirot P, Gouello JP, Mathieu E, Vincent JF, Alquier P. Adreno-cortical function during septic shock. *Intensive Care Med.* 1995;21:57-62.
19. Soni A, Pepper GM, Wyrwinski PM, Ramirez NE, Simon R, Pina T, et al. Adrenal insufficiency occurring during septic shock: incidence, outcome, and relationship to peripheral cytokine levels. *Am J Med.* 1995;98:266-71.
20. Hatherill M, Tibby SM, Hilliard T, Turner C, Murdoch IA. Adrenal insufficiency in septic shock. *Arch Dis Child.* 1999;80:51-5.
21. Rothwell PM, Udawadia ZF, Lawler PG. Cortisol response to corticotropin and survival in septic shock. *Lancet.* 1991; 337:582-3.
22. Rivers EP, Gaspari M, Saad GA, Mlynarek M, Fath J, Horst HM, et al. Adrenal insufficiency in high-risk surgical ICU patients. *Chest.* 2001;119:889-96.
23. Rydvall A, Brandstrom AK, Banga R, Asplund K, Backlund U, Stegmayr BG. Plasma cortisol is often decreased in patients treated in an intensive care unit. *Intensive Care Med.* 2000; 26:545-51.
24. Menon K, Clarson C. Adrenal function in pediatric critical illness. *Pediatr Crit Care Med.* 2002;3:112-6.
25. Loisa P, Rinne T, Kaukinen S. Adrenocortical function and multiple organ failure in severe sepsis. *Acta Anaesthesiol Scand.* 2002;4:145-51.
26. Sibbald WJ, Short A, Cohen MP, Wilson RF. Variations in adrenocortical responsiveness during severe bacterial infections. Unrecognized adrenocortical insufficiency in severe bacterial infections. *Ann Surg.* 1977;186:29-33.
27. Beishuizen A, Thijs LG. Relative adrenal failure in intensive care: an identifiable problem requiring treatment? *Best Pract Res Clin Endocrinol Metab.* 2001;4:513-31.
28. Grinspoon SK, Biller BM. Clinical review 62: Laboratory assessment of adrenal insufficiency. *J Clin Endocrinol Metab.* 1994;79:923-31.
29. Schein RM, Sprung CL, Marcial E, Napolitano L, Chernow B. Plasma cortisol levels in patients with septic shock. *Crit Care Med.* 1990;18:259-63.
30. Sam S, Corbridge TC, Mokhlesi B, Comellas AP, Molitch ME. Cortisol levels and mortality in severe sepsis. *Clin Endocrinol (Oxf).* 2004;60:29-35.
31. Bollaert PE, Fieux F, Charpentier C, Lévy B. Baseline cortisol levels, cortisol response to corticotropin, and prognosis in late septic shock. *Shock.* 2003;19:13-5.
32. Bone M, Diver M, Selby A, Sharples A., Addison M, Clayton P. Assessment of adrenal function in the initial phase of meningococcal disease. *Pediatrics.* 2002;110:563-9.
33. Oelkers W. Adrenal insufficiency. *N Engl J Med.* 1996;335:1206-12.
34. Journey TH, Cockrell JL, Lindberg JS, Lamiell JM, Wade CE. Spectrum of serum cortisol response to ACTH in ICU patients. Correlation with degree of illness and mortality. *Chest.* 1987; 92:292-5.
35. Finlay WE, McKee JI. Serum cortisol levels in severely stressed patients. *Lancet.* 1982;19:1414-5.
36. Marik PE, Zaloga GP. Adrenal Insufficiency during septic shock. *Crit Care Med.* 2003; 31:141-45.
37. Langer M, Modi PB, Agus M. Adrenal insufficiency in the critically ill neonate and child. *Curr Opin Pediatr.* 2006;18:448-53.
38. Siraux V, De Backer D, Yalavatti G, Mélot C, Gervy C, Mockel J. Relative adrenal insufficiency in patients with septic shock: comparison of low-dose and conventional corticotropin tests. *Crit Care Med.* 2005;33:2479-86.
39. Dorin RI, Qualls CR, Crapo LM. Diagnosis of adrenal insufficiency. *Ann Intern Med.* 2003;139:194-204.
40. Hamrahan AH, Oseni TS, Arafah BM. Measurements of serum free cortisol in critically ill patients. *N Engl J Med.* 2004; 350:1629-38.
41. Perla D, Marmorston J. Suprarenal cortical hormone and salt in the treatment of pneumonia and other severe infections. *Endocrinology.* 1940;27:367-74.
42. Hahn EO, Houser HB, Rammelkamp CH Jr, Denny FW, Wannamaker LW. Effect of cortisone on acute streptococcal infections and post-streptococcal complications. *J Clin Invest.* 1951;30:274-81.
43. Matot I, Sprung CL. Corticosteroids in septic shock: resurrection of the last rites? *Crit Care Med.* 1998;26:627-30.
44. Sessler CN. Steroids for septic shock: back from the dead? (Con). *Chest.* 2003;123:482S-9S.
45. Balk RA. Steroids for septic shock: back from the dead? (Pro). *Chest.* 2003;123:490S-9S.
46. Annane D. Corticosteroids for septic shock. *Crit Care Med.* 2001; 29:S117-20.
47. Luce JM, Montgomery AB, Marks JD, Turner J, Metz CA, Murray JF. Ineffectiveness of high-dose methylprednisolone in preventing parenchymal lung injury and improving mortality in patients with septic shock. *Am Rev Res Dis.* 1988;138:62-8.
48. Effect of high-dose glucocorticoid therapy on mortality in patients with clinical signs of sepsis The Veterans Administration Systemic Sepsis Cooperative Study Group. *N Engl J Med.* 1987;317:659-65.
49. Bone RC, Fisher CJ Jr, Clemmer TP, Slotman GJ, Metz CA, Balk RA. A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. *N Engl J Med.* 1987;317:653-8.
50. Sprung CL, Caralis PV, Marcial EH, Pierce M, Gelbard MA, Long WM, et al. The effect of high-dose corticosteroids in patients with septic shock. A prospective, controlled study. *N Engl J Med.* 1984;311:1137-43.
51. Thompson WT, Gurley HT, Lutz BA. Inefficacy of corticosteroids in shock (double-blind study). [Abstract]. *Clin Res.* 1976; 24:258A.
52. Lucas CE, Ledgerwood AM. The cardiopulmonary response to massive doses of steroids in patients with septic shock. *Arch Surg.* 1984;119:537-41.
53. Schumer W. Steroids in the treatment of clinical septic shock. *Ann Surg.* 1976;184:333-41.
54. Klastersky J, Cappel R, Debusscher L. Effectiveness of betamethasone in management of severe infections. A double-blind study. *N Engl J Med.* 1971;284:1248-50.
55. Bennett IL, Finland M, Hamburger, Kass EH, Lepper M, Waisbren BA. The effectiveness of hydrocortisone in the management of severe infections. *JAMA.* 1963;183:462-5.
56. Rogers J. Large doses of steroids in septic shock. *Br J Urol.* 1970;42:742.

57. Bollaert PE, Charpentier C, Levy B, Debouverie M, Audibert G, Larcan A. Reversal of late septic shock with supraphysiologic doses of hydrocortisone. *Crit Care Med.* 1998;26:645-50.
58. Briegel J, Forst H, Haller M, Schelling G, Kilger E, Kuprat G, et al. Stress doses of hydrocortisone reverse hyperdynamic septic shock: a prospective, randomized, double-blind, single center study. *Crit Care Med.* 1999;27:723-32.
59. Keh D, Boehnke T, Weber-Cartens S, Schulz C, Ahlers O, Bercker S, et al. Immunologic and hemodynamic effects of "low-dose" hydrocortisone in septic shock: a double-blind, randomized, placebo-controlled, crossover study. *Am J Respir Crit Care Med.* 2003;167:512-20.
60. Chawla K, Kupfer Y, Tessler S. Hydrocortisone reverses refractory septic shock. *Crit Care Med.* 1999;27:A33.
61. Oppert M, Schindler R, Husung C, Offermann K, Gräf KJ, Boenisch O, et al. Low-dose hydrocortisone improves shock reversal and reduces cytokine level in early hyperdynamic septic shock. *Crit Care Med.* 2005;33:2457-64.
62. Carcillo JA, Fields AI; American College of Critical Care Medicine Task Force Committee Members. Clinical practice parameters for hemodynamic support of pediatric and neonatal patients in septic shock. *Crit Care Med.* 2002;30:1365-78.
63. Sumarmo. The role of steroids in dengue shock syndrome. *Southeast Asian J Trop Med Public Health.* 1987;18:383-9.
64. Min M, U T, Aye M, Shwe TN, Swe T. Hydrocortisone in the management of dengue shock syndrome. *Southeast Asian J Trop Med Public Health.* 1975;6:573.
65. Hildebrandt T, Mansour M, Al Samsam R. The use of steroids in children with septicemia: review of the literature and assessment of current practice in PICUs in the UK. *Pediatr Anesth.* 2005; 15:358-65.

Correspondence:

Cristiane Freitas Pizarro  
Unidade de Terapia Intensiva Pediátrica  
Av. Dr. Enéas de Carvalho Aguiar, 647  
CEP 05403-900 – São Paulo, SP – Brazil  
Tel.: +55 (11) 3256.4638  
E-mail: crispizarro@terra.com.br