# Absolute and relative adrenal insufficiency in children with septic shock*

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***Objective:*** **Corticosteroid replacement improves outcome in adults with relative adrenal insufficiency and catecholamine-resistant septic shock. We evaluated the relationship of absolute and relative adrenal insufficiency to catecholamine-resistant septic shock in children.**

***Design:*** **Prospective cohort study.**

***Setting:*** **University hospital pediatric intensive care unit in Brazil.**

***Patients:*** **Fifty-seven children with septic shock. Children with HIV infection, those with a history of adrenal insufficiency, and those submitted to any steroid therapy or etomidate within the week before diagnosis of septic shock were excluded.**

***Interventions:*** **None.**

***Measurements and Main Results:*** **A short corticotropin test (250 μg) was performed, and cortisol levels were measured at baseline and 30 and 60 mins posttest. Adrenal insufficiency was defined by a response ≤9 μg/dL. Absolute adrenal insufficiency was further defined by a baseline cortisol <20 μg/dL and relative adrenal insufficiency by a baseline cortisol >20 μg/dL. Absolute adrenal insufficiency was observed in 18% of children, all of whom had catecholamine-resistant shock. Relative adrenal insufficiency was observed in 26% of children, of whom 80% had catecholamine-resistant and 20% had dopamine/dobutamine-responsive shock. All children with fluid-responsive shock had a cortisol response >9 μg/dL. Children with adrenal insufficiency had an increased risk of catecholamine-resistant shock (relative risk, 1.88; 95% confidence interval, 1.26–2.79). However, mortality was independently predicted by chronic illness or multiple organ failure ($p < .05$), not adrenal insufficiency.**

***Conclusions:*** **Absolute and relative adrenal insufficiency is common in children with catecholamine-resistant shock and absent in children with fluid-responsive shock. Studies are warranted to determine whether corticosteroid therapy has a survival benefit in children with relative adrenal insufficiency and catecholamine-resistant septic shock. (Crit Care Med 2005; 33:855–859)**

**KEY WORDS: septic shock; sepsis; adrenal insufficiency; shock; corticosteroids; cortisol.**

Septic shock is a major cause of mortality in pediatric and adult intensive care units (1). In this regard, the role of corticosteroid therapy in the management of septic shock has been extensively debated for many years. Recently, investigators have reported hemodynamic and survival benefits associated with the use of more physiologic steroid replacement therapy in adult patients with relative adrenal insufficiency and vasopressor-dependent septic shock (2, 3).

Adequate adrenocortical function is essential to survive critical illness, and most critically ill patients display an elevated plasma cortisol level, reflecting activation of the pituitary-adrenal-axis, which is considered to be a homeostatic adaptation. Over the past decade, investigators have found that many adults with vasopressor-dependent septic shock have elevated cortisol levels but a depressed response to stimulation with 250 μg of corticotropin (cortisol increment ≤9 μg/dL) (2). This state of "relative" adrenal insufficiency is characterized by an inadequate production of cortisol in relation to an increased demand during periods of severe stress. However, the incidence, importance, and therapeutic approach to adrenal insufficiency in critically ill children are less understood than in adults (4, 5).

Hatherill et al. (6) and Menon and Clarson (7) studied the incidence of adrenal insufficiency in critically ill children. Hatherill et al. reported that 33 children with septic shock had a 52% incidence of adrenal insufficiency with an increased inotrope and vasopressor requirements but no increase in mortality compared with those without adrenal insufficiency (6). Menon and Clarson reported a 31% incidence of adrenal insufficiency in 13 critically ill children (7). In the present study, we administered a short corticotropin stimulation test to children with septic shock to determine the incidence of absolute and relative adrenal insufficiency and to evaluate the relationship of adrenal function to the development of catecholamine-resistant shock and outcome.

## MATERIALS AND METHODS

*Study Population.* We enrolled consecutive eligible children admitted to the pediatric intensive care unit (PICU) of Instituto da Criança Pedro de Alcântra da Faculdade de Medicina da Universidade de São Paulo, Brazil, between January 2001 and June 2003 who fulfilled criteria for septic shock according to international guidelines published in 2002 by the American College of Critical Care Medi-

*See also p. 911.

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cine (ACCM) for hemodynamic support of children and newborns with septic shock (8). The clinical diag=nosis of septic shock was made in children who a) had suspected infection manifested by hypothermia or hyperthermia; and b) had clinical signs of decreased perfusion including decreased mental status, prolonged capillary refill >2 secs (cold shock) or bounding (warm shock) peripheral pulses, mottled cool extremities (cold shock), or decreased urine output <1 $cm^3$/kg. Although hypotension was not necessary for the diagnosis, its presence was confirmatory.

Patients were ineligible for the study if they had human immunodeficiency virus (HIV) infection, had a history of adrenal insufficiency, or had received steroids or etomidate within the week before the diagnosis of septic shock. The protocol was approved by our institutional review board, and informed consent was obtained from the patient's next of kin.

*Data Collection.* Demographic information included age, gender, ethnic group, admission diagnosis, presence of chronic disease, multiple organ system failure score at admission and peak multiple-organ failure score during the stay in PICU (9, 10), pediatric risk of mortality score, and calculated risk of mortality (11).

Clinical information included inotrope, vasopressor, and vasodilator use; duration of shock; duration of positive pressure ventilation; length of stay in PICU; and serum sodium, potassium, and glucose levels.

Adrenal function was assessed by the cortisol response to synthetic adrenocorticotropic hormone stimulation. In the first 24 hrs after the diagnosis of septic shock, baseline cortisol was measured and the short corticotropin test (Cosyntropin, Organon, West Orange, NJ) was performed using a dose of 250 μg of corticotropin. Serum cortisol concentrations were evaluated at 30 and 60 mins afterward. Plasma cortisol concentrations were determined by fluoroimmunoassay. The peak cortisol concentration was taken as the maximum concentration at either 30 or 60 mins, and the cortisol increment was calculated as the peak minus baseline value. Clinicians were blinded to the results of the cortisol testing until after study completion.

The children were classified in four groups according to adrenal function:

Absolute adrenal insufficiency (group 1): baseline cortisol <20 μg/dL and increment ≤9 μg/dL

Relative adrenal insufficiency (group 2): baseline cortisol ≥20 μg/dL and an increment ≤9 μg/dL

Adequate adrenal response with an elevated baseline cortisol (group 3): baseline cortisol ≥20 μg/dL and an increment >9 μg/dL

Adequate adrenal response without an elevated baseline cortisol (group 4): baseline cortisol <20 μg/dL and an increment >9 μg/dL

The children were also classified in three groups according to need for cardiovascular support according to ACCM definitions:

Fluid-responsive shock (group A): shock that reversed with 60 mL/kg isotonic crystalloid or colloid fluid resuscitation in 1 hr

Fluid refractory dopamine/dobutamine-responsive shock (group B): shock that reversed with 60 mL/kg isotonic crystalloid or colloid fluid resuscitation and ≤10 μg/kg/min of dopamine and/or dobutamine infusion

Catecholamine-resistant shock (group C): shock that persisted despite the use of catecholamines epinephrine or norepinephrine

*Statistical Analysis.* Data were analyzed using the Epi-info (version 6.04b) and Statistical Package for the Social Sciences (SPSS) for Windows (version 10.0) software programs.

Patient characteristics were described using means, standard deviations, medians, and proportions. Clinical characteristics were all compared by Kruskal-Wallis (four groups) and by Mann-Whitney tests (two groups). The relationship between the categorical variables and shock response to catecholamines (refractory × responsive) or survival was analyzed by the chi-square or Fisher's exact tests. Univariate and multiple logistic regression models were constructed, and the dependent variables were shock response to catecholamines and survival. The cut point of $p < .10$ in the univariate analysis was selected for the multiple regression analyses. The stepwise backward selection procedure was used, and the variables were kept in the model when $p < .05$ and/or when considered confounders. The adequacy of fit of the final multiple variable model was evaluated by the Hosmer-Lemeshow test.

## RESULTS

We enrolled 57 children with septic shock into the study. Their median age was 27.0 months (range, 1–213 months), and their gender distribution was 60% female and 40% male. Chronic disease was present in 74% of patients, and the most frequent diagnosis was oncologic (16%) followed by hepatic (14%) and neurologic (11%) diseases. Overall mortality was 39%, with mortality being 0% (n = 0 of 8) in fluid-responsive shock patients, 17% (n = 2 of 12) in dopamine/dobutamine-responsive shock patients, and 54% (n = 20 of 37) in children with catecholamine-resistant shock ($p < .05$). The specific fluid, inotrope, and vasopressor requirements in these patients are summarized in Table 1.

The incidence of adrenal insufficiency in our study population was 44% (95% confidence interval, 31.1%-56.9%) as defined by a response ≤9 μg/dL posttest. Table 2 shows the incidence of adrenal insufficiency in our population when using six different sets of criteria published in six prior studies. Using these criteria, the incidence of adrenal insufficiency in our population ranged from 9% to 44%.

The incidence of absolute adrenal insufficiency was 18%, and the incidence of relative adrenal insufficiency was 26% (Table 3). The baseline and peak postcorticotropin stimulation cortisol levels are summarized in Table 3. The clinical characteristics of the patients in the four adrenal function groups are shown in Table 3. There were no significant differences in serum sodium, potassium, and glucose levels. There was no difference in duration of positive-pressure ventilation, shock, or length of stay in the PICU; however, there were significant differences in the age and multiple organ system failure score during the PICU stay among the four groups. With regard to infection, the following microorganisms were isolated in cultures (including blood, urine, pleural, and ascitic fluid):

**Table 1.** Fluid resuscitation (mL/kg) and inotrope and vasopressor dosage (μg/kg/min) given to patients with sepsis or septic shock

| Variable | No. of Patients | Median | Range |
|---|---|---|---|
| Fluid requirement, mL/kg | | | |
| Fluid-responsive shock | 8 | 50 | 10–120 |
| Fluid-refractory shock | 49 | 60 | 20–120 |
| Inotrope and vasopressor requirement, μg/kg/min | | | |
| Dopamine | 42 | 12.5 | 5.0–20.0 |
| Dobutamine | 28 | 10.0 | 5.0–22.0 |
| Epinephrine | 8 | 1.5 | 0.8–5.0 |
| Norepinephrine | 21 | 0.9 | 0.1–4.0 |

Gram-positive, 21% (n = 12); Gram-negative (other than *Neisseria meningitidis*), 14% (n = 8); fungus, 9% (n = 5); and mixed agents, 16% (n = 9).

All children with fluid responsive shock had a corticotropin response >9 μg/dL (Fig. 1, $p < .05$). Chi-square test for trend revealed a significant association between inotrope/vasopressor requirement group and adrenal function group (Fig. 1, $p = .009$). Combining groups 1–2 and 3–4, the relative risk of catecholamine-resistant shock was 1.88 (95% confidence interval, 1.26–2.79) for groups 1–2 compared with groups 3–4 ($p = 0.01$). Stepwise regression analysis showed that adrenal dysfunction (corticotropin response <9 μg/dL) and multiple organ failure independently predicted catecholamine resistant shock ($p < .05$).

Chi-square test for trend was not significant between adrenal function group and mortality (Fig. 2, $p = .08$). Combining groups 1–2 and 3–4, the relative risk of death was not significant (1.72, 95% confidence interval, 0.97–3.06) for groups 1–2 when compared with groups 3–4 ($p = .12$). Univariate analysis showed that chronic disease, multiple organ system failure, and catecholamine-resistant shock predicted death ($p < .05$). Stepwise regression analysis showed that chronic illness and multiple organ failure at admission, not adrenal dysfunction (absolute and relative adrenal insufficiency), predicted outcome ($p < .05$).

**Table 2.** Incidence of adrenal insufficiency in our study population and the according to the various published definitions

| Adrenal Insufficiency Definitions | | Adrenal Insufficiency Incidence | |
|---|---|---|---|
| Author (Yr) | Cortisol Level (μg/dL) | According to Literature, % | In Our Study Population, % |
| Rothwell *et al.* (1991) | Increment <9 after ACTH stimulation test | 40 | 44 |
| Hatherill *et al.* (1999) | Increment <7,5 after ACTH stimulation test | 52 | 37 |
| Soni *et al.* (1995) | Cortisol <18 after ACTH stimulation test | 24 | 9 |
| Marik & Zaloga (2001) | Baseline cortisol <25 and peak cortisol <25 | 61 | 28 |
| Loisa *et al.* (2002) | Baseline cortisol <25 and increment ≤9 | 15 | 21 |
| Menon & Clarson (2002) | Baseline cortisol <7 or cortisol <18 after ACTH stimulation test | 31 | 9 |

ACTH, Adrenocorticotropic hormone.

## DISCUSSION

Absolute and relative adrenal insufficiencies were both common in children with catecholamine-resistant shock. Three indirect lines of evidence support, but do not prove, the possibility that adrenal dysfunction contributed in part to the development of catecholamine-resistant shock in our patients. First, all the children with fluid-responsive shock had a normal adrenal response to corticotropin. Second, there was an independent association between the inability to mount a >9 μg/dL cortisol response to the short corticotropin stimulation test and the development of catecholamine-resistant shock. Third, all patients with absolute adrenal insufficiency had catecholamine-resistant shock (12–15).

There are no established and accepted criteria to define adrenal insufficiency in critically ill patients. The stated incidence of adrenal insufficiency in our population varies according to what set of published criteria are used. It could be as low as 9% and as high 44% according to these studies (6, 7, 16–19) (Table 2). The criteria we have used, taking into account a cortisol response ≤9 μg/dL, appear to be the most inclusive (2, 16). We adopted a cortisol cutoff before and after corticotropin stimulation test of 20 μg/dL (550 nmol/L) (20–22).

The rapid corticotropin stimulation test is widely used as a simple method to identify adrenocortical hyporesponsiveness, but there is an ongoing debate about the dose to be used and the timing for measurement of plasma cortisol. The 250-μg corticotropin dose is standard, but a low dose of 1 μg for the cortico-

**Table 3.** Clinical characteristics in the four adrenal function groups

| Variables | Absolute Adrenal Insufficiency n = 10 | Relative Adrenal Insufficiency n = 15 | Adequate Response | | *p* Value |
|---|---|---|---|---|---|
| | | | Cortisol ≥20 μg/dL n = 15 | Cortisol <20 μg/dL n = 17 | |
| Age, months | 75.5 (16–213) | 47.0 (3–201) | 5.0 (1–91) | 23 (4–175) | .01 |
| Risk of mortality, % | 17.6 (0.56–98.6) | 10.0 (1.63–81.9) | 10.8 (2.36–88.8) | 6.7 (0.36–94.1) | .76 |
| Admission MOSF score | 2.5 (0–6) | 2.0 (1–3) | 2.0 (0–4) | 1.0 (0–3) | .11 |
| MOSF score during PICU stay | 3.5 (1–7) | 2.0 (1–5) | 2.0 (0–4) | 1.0 (0–4) | .02 |
| Level sodium, mg/dL | 136.5 (119.5–154) | 140.5 (118.5–159) | 136.5 (122–140) | 138 (127–192) | .22 |
| Level potassium, mg/dL | 4.2 (3.3–6.0) | 3.7 (1.5–5.5) | 3.9 (2.5–6.8) | 4.2 (1.9–5.9) | .52 |
| Level glucose, mg/dL | 90.0 (10–147) | 88.3 (47–411) | 102 (23–339) | 114.5 (19–233.5) | .80 |
| Duration of positive pressure ventilation, days | 3.5 (0–25) | 4.0 (0–14) | 4.0 (0–17) | 2.0 (0–46) | .92 |
| Time shock, days | 3.5 (1–11) | 4.0 (0–9) | 3.0 (0–12) | 2.0 (0–16) | .86 |
| Length of stay in PICU, days | 7.0 (1–37) | 8.0 (0–20) | 12.0 (0–18) | 6.0 (1–49) | .68 |
| Baseline cortisol, μg/dL | 15.3 (6–18) | 37.8 (22–91) | 35.1 (23–51) | 14.4 (7–19) | <.001 |
| Peak cortisol, μg/dL | 18.5 (6–23) | 36 (23–51) | 60.5 (37–80) | 31 (22–52) | <.001 |

Values are expressed as median (range).

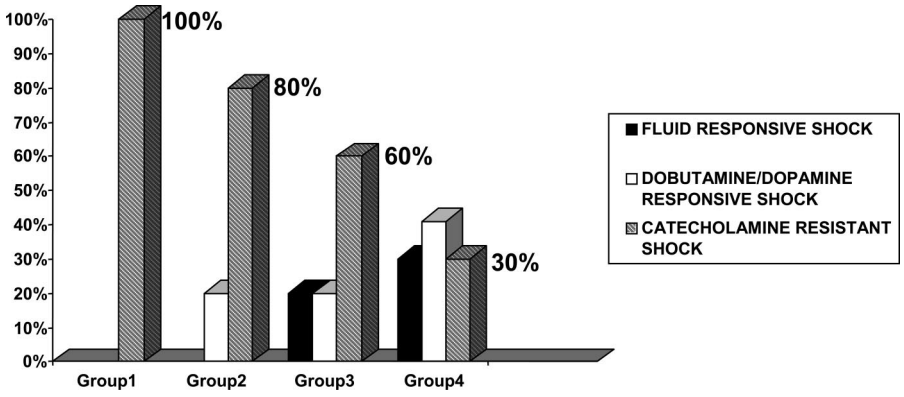


**Figure 1.** Response to fluid and catecholamine therapy was related to adrenal function (chi-square analysis for trend $p < .009$). Group 1, absolute adrenal insufficiency; group 2, relative adrenal insufficiency; group 3, adequate adrenal response with baseline cortisol level ≥20 μg/dL; group 4, adequate adrenal response with baseline cortisol level <20 μg/dL.

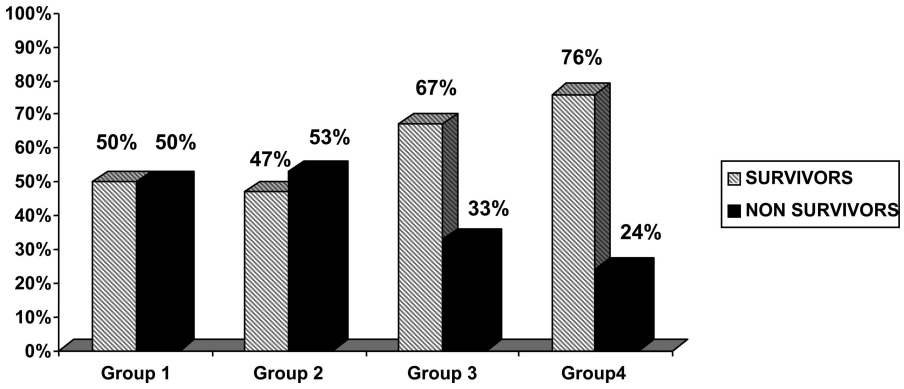


**Figure 2.** Outcome was not related to adrenal function (chi-square analysis for trend $p = .08$). Group 1, absolute adrenal insufficiency; group 2, relative adrenal insufficiency; group 3, adequate adrenal response with baseline cortisol level ≥20 μg/dL; group 4, adequate adrenal response with baseline cortisol level <20 μg/dL.

tropin stimulation test has recently been proposed with the suggestion that it may be more sensitive. We chose to use the traditional standard for the corticotropin stimulation test since further validation was necessary, at the time our study began, for the low-dose test (18, 23–25).

Adrenal insufficiency was associated with worsening of multiple organ failure in our pediatric population. Loisa et al. (19) similarly found a relationship between decreased adrenal response to corticotropin and development of more severe multiple organ failure in adults with septic shock. The explanation of this finding remains a matter of investigation. Plasma from septic subjects as well as tumor necrosis factor-α inhibits adrenal synthesis of cortisol (4, 18, 26, 27). It appears that excessive systemic inflammation is the pathophysiologic hallmark of adrenal as well as other organ dysfunction in patients with septic shock and severe sepsis.

Annane et al. (2) previously reported that baseline cortisol level and corticotropin-stimulated cortisol level increment prognosticated outcome in adults with vasopressor-dependent septic shock. Specifically, patients with a baseline <34 μg/dL and an increment <9 μg/dL had a good prognosis (26% mortality); patients with a baseline cortisol <34 μg/dL and an increment < μg/dL or a baseline >34 μg/dL and an increment >9 μg/dL had an intermediate prognosis (mortality 67%); and patients with a baseline cortisol >34 μg/dL and an increment <9 μg/dL had a poor prognosis (82% mortality). In our population, a good prognosis (24% mortality) was observed in children with baseline cortisol <20 μg/dL and increment >9 μg/dL; an intermediate prognosis (33% mortality) was observed with baseline ≥20 μg/dL and increment >9 μg/dL; and a poor prognosis was observed in children with a baseline cortisol <20 μg/dL and increment ≤9 μg/dL (50% mortality) or baseline cortisol ≥20 μg/dL and increment ≤9 μg/dL (53% mortality). Interestingly, Annane and colleagues reported no absolute adrenal insufficiency in their adult cohort. The explanation for this may be an age-related phenomenon since absolute adrenal insufficiency was more common in the children in our cohort study.

*Absolute and relative adrenal insufficiency is common in children with catecholamine-resistant shock.*

On the other hand, we showed that in the pediatric population, the contribution of adrenal insufficiency to mortality was not evident, particularly when controlling for chronic disease and multiple organ failure. These findings are similar to the previous report by Hatherill et al. (6)

## CONCLUSIONS

Absolute and relative adrenal insufficiency is common in children with septic shock and may contribute to the development of catecholamine-resistant shock; in others words, it is associated with an increased vasopressor requirement. However, doubts still persist regarding the efficacy of replacement therapy with low-dose steroids in children with catecholamine-resistant septic shock, and further studies are needed to determine whether treatment of such patients changes morbidity and/or mortality (28, 29).

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