Adrenal status in children with septic shock using low-dose stimulation test*

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LEARNING OBJECTIVES

On completion of this article, the reader should be able to:

1. Define the controversies surrounding the definition of adrenal dysfunction in children with septic shock.
2. Identify clinical factors in children with septic shock that are associated with relative adrenal insufficiency.
3. Recall the relationship between catecholamine refractory shock and relative adrenal insufficiency in children with septic shock.

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Objectives: **There is paucity of data on the magnitude of absolute or relative adrenal insufficiency in septic shock, especially in children. We conducted a prospective study to determine the prevalence of adrenal insufficiency in children with septic shock using a low-dose Synacthen (1 μg) stimulation test.**

Design: **Cross-sectional study.**

Setting: **Pediatric intensive care unit in a tertiary care hospital in northern India.**

Patients: **Children with septic shock.**

Interventions: **None.**

Measurements and Main Results: **We performed cortisol estimation at baseline and after low-dose Synacthen (1 μg) stimulation at 30 and 60 mins in children with fluid refractory septic shock admitted to our pediatric intensive care unit. Basal cortisol levels <7 μg/dL and peak cortisol level <18 μg/dL were used to define adrenal insufficiency. An increment of <9 μg/dL after stimulation was used to diagnose relative adrenal insufficiency. As there is lack of consensus on the cutoffs for defining relative adrenal insufficiency using the low-dose adrenocorticotropic hormone test, we evaluated different cutoff values (increment at 30 mins, increment at 60 mins, greater of the two increments) and evaluated their association with the incidence of catecholamine refractory shock and outcomes. Children with sepsis but without septic shock were sampled for baseline cortisol levels as a comparison. Thirty children (15 girls) with septic shock were included; median age (95% confidence interval) was 36.5 (9.39– 58.45) months. Median Pediatric Risk of Mortality score was 22.5 (14.13–24.87). Fifteen (50%) children survived. The median (95% confidence interval) cortisol values at baseline and 30 mins and 60 mins after stimulation were 71 (48.74–120.23) μg/dL, 78.1 (56.9–138.15) μg/dL, and 91 (56.17–166.44) μg/dL, respectively. The median baseline cortisol value in age- and gender-matched children with sepsis was 11.5 μg/dL. None of the children with septic shock fulfilled the criteria for absolute adrenal insufficiency. However, nine (30%) patients had relative adrenal insufficiency (increment in cortisol <9 μg/dL). Of these nine patients, five (56%) died; of the 21 patients with a greater increment in cortisol after stimulation, ten died ($p = .69$). Compared with patients in septic shock with normal adrenal reserve, those with relative adrenal insufficiency had a higher incidence of catecholamine refractory shock ($p = .019$) but no difference in mortality rate ($p = .69$). On the sensitivity and specificity analysis using various cutoffs of increment, the best discrimination for catecholamine refractory shock was obtained with a peak increment <6 μg/dL.**

Conclusions: **Relative adrenal insufficiency is common in children with septic shock and is associated with catecholamine refractory shock. (Pediatr Crit Care Med 0; 8:●●●–●●●)**

KEY WORDS: septic shock; cortisol; adrenal insufficiency

Septic shock is an important cause of mortality in pediatric intensive care units (1). Many patients have fluid and catecholamine refractory septic shock, and adrenal insufficiency may be a contributor to this phenomenon. Data from studies in adults suggest that treatment with glucocorticoids improves the outcome (2). Whether the same is applicable to children needs evaluation.

There is paucity of data on the magnitude of adrenal insufficiency in septic shock, especially in children. Hatherill et al. (3) and Menon and Clarson (4) studied the incidence of adrenal insufficiency in children with septic shock and critically ill children, respectively. Hatherill et al. reported a 52% incidence of adrenal insufficiency in 33 children with septic shock, whereas Menon and Clarson reported a 31% incidence of adrenal insufficiency in 13 critically ill children.

***See also p. xx.**

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Table 1. Prevalence of adrenal insufficiency in our patients according to criteria used in various published studies

Definition of Adrenal Dysfunction, Cortisol, μg/dL	References	Adrenal Insufficiency	
		No.	%
Increment <9	10, 11	9	30
Baseline <5	12	0	0
Baseline <7	4, 13, 14	0	0
Basal cortisol <20, increment ≤9	15	0 and 9	0 and 30
Increment <7	3, 16–19	5	16.7
Peak <18	4, 19, 20	0	0
Peak <18 and increment <7	17	0	0
Peak <(baseline × 2)	19, 21	27	90

Whereas the baseline serum cortisol values give information about absolute adrenal insufficiency, stimulation tests are used to evaluate the adrenal reserve. Adrenal insufficiency may be associated with poor response to catecholamines.

There is need to assess the prevalence of adrenal insufficiency in children with septic shock so as to define the need for steroid replacement therapy. Earlier studies used a high dose of corticotropin (125–250 μg) for stimulation of adrenals; this has been considered a pharmacologic dose, especially in small children (5). Such a high supraphysiologic dose can override adrenal resistance to adrenocorticotropic hormone (ACTH) and result in a normal cortisol response, even in patients with acute secondary adrenal insufficiency (6). Moreover, a patient may have an appropriately high serum cortisol concentration but be unable to respond further after corticotropin injection (no reserve). Low-dose stimulation tests may be more sensitive in detecting relative adrenal insufficiency. However, there is lack of consensus on the cutoffs to be used for these tests.

We conducted a prospective study to determine the prevalence of absolute and relative adrenal insufficiency in children with fluid refractory septic shock using a 1-μg dose of synthetic ACTH analogue.

METHODS

We performed a prospective study in the Intensive Care Unit, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, between January 2004 and February 2005.

We enrolled critically ill children with septic shock who did not respond to a fluid challenge of 60 mL/kg of isotonic fluids administered in the first hour (1, 7, 8).

Patients already receiving steroids or who received steroids in past 6 months, patients with primary adrenal insufficiency, children with chronic organ dysfunction/chronic illness, children with known hypothalamic/pituitary dysfunction, and patients receiving phenytoin, phenobarbitone, or rifampicin were excluded.

The study protocol was approved by the Ethics Committee of our institute. Children were enrolled soon after a diagnosis of fluid refractory septic shock was made, after obtaining a written informed consent from the parent or guardian.

We collected demographic information including age, gender, admission diagnosis, Pediatric Risk of Morality (PRISM) score (9), and physiologic variables. We collected data on use of vasoactive drugs, duration of shock, and blood investigation reports.

We performed serum cortisol estimation at baseline (soon after a diagnosis of fluid refractory septic shock was made) and after low-dose Synacthen (1 μg) stimulation at 30 and 60 mins. Two milliliters of blood was drawn at baseline and 30 and 60 mins after intravenous injection of Synacthen (1 μg), and serum was separated. We did not obtain the cortisol levels at any specific time of the day as most critically ill patients lose the diurnal variation in their cortisol values (5). Cortisol was estimated using the DPC IMMULITE chemiluminescent immunoassay (DPC, Los Angeles, CA), where an enhanced chemiluminescence technique is used (measurable range, 1–50 μg/dL; minimum analytical sensitivity, 0.2 μg/dL; coefficient of variation 10%). The specimens were diluted, and the assays were repeated if the cortisol values were >50 μg/dL. 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 the baseline value. The treating team was blinded to the results of the cortisol testing until after study completion. The patients were managed according to standard treatment protocol (1). No changes in the standard treatment protocol were made based on the results of the adrenal function tests. Children with catecholamine refractory shock received hydrocortisone (100 mg/m^2/day in four divided doses intravenously). Patients were diagnosed to have catecholamine refractory shock if shock persisted despite the use of catecholamines—epinephrine or norepinephrine (1). The results of cortisol assays were not available for deciding about use of steroids in any patient.

We estimated baseline cortisol in children with sepsis who were matched for age and gender with enrolled children for septic shock.

Basal cortisol levels <7 μg/dL and/or peak cortisol level (higher of the values of cortisol at 30 or 60 mins after stimulation) <18 μg/dL were used to define adrenal insufficiency (4). We considered diagnosis of relative adrenal insufficiency if the increment in cortisol was <9 μg/dL after stimulation (greater of the increment at 30 or 60 mins after stimulation) (10, 11). Various other definitions have been used by different authors (3, 4, 10–21) (Table 1).

As there is lack of consensus on the appropriate cutoffs with the use of low-dose stimulation tests, we evaluated the association of catecholamine refractory shock and mortality with different levels of increment in cortisol after stimulation (increment at 30 mins, increment at 60 mins, maximum increment).

The data were managed on Excel spreadsheet and analyzed using STATA 7.0 (Stata, College Station, TX). Patient characteristics were expressed as means, standard deviations, medians, and proportions. For comparing the differences in continuous variables, we used Mann–Whitney test or *t*-test. The relationship between categorical variables was analyzed using chi-square or Fisher's exact test.

RESULTS

We studied the adrenal status in 30 children (15 girls) with fluid refractory septic shock. The median age of our study subjects was 36.5 months (95% confidence interval [CI], 9.39–58.45 months). Median PRISM score was 22 (95% CI, 14–25). Sixty percent of the study patients had pneumonia, 43% meningitis, and 36% gastrointestinal infections; some patients had more than one focus. Only four patients had a positive blood culture report: Three grew *Escherichia coli* and one grew *Staphylococcus aureus*. Culture specimen from other sites grew *E. coli* in bronchoalveolar lavage fluid in one, *S. aureus* in pleural fluid in one, and *Acinetobacter* in peritoneal fluid in one. Most of the children were malnourished: median weight for age z score of −2 (95% CI, −2.8 to −1).

The basal cortisol levels were high in children with septic shock, ranging from 24.5 to 269.5 μg/dL, and median basal cortisol level was 71 (95% CI, 48.74–

120.23) μg/dL. The median basal cortisol value in age- and gender-matched children with sepsis (median PRISM score, 5) was 11.5 μg/dL. The median cortisol values at 30 and 60 mins after stimulation in children with septic shock were 78.1 (56.9–138.15) μg/dL and 91 (56.17–166.44) μg/dL, respectively. The median peak increase in cortisol levels from basal after stimulation with 1 μg of Synacthen at either 30 or 60 mins was 13.4 μg/dL (95% CI, 9.3–37.68).

None of the study subjects with septic shock had absolute adrenal insufficiency using the definition mentioned in the Methods section. The prevalence of adrenal insufficiency with various definitions used by different authors is shown in Table 1. Figure 1 shows the study profile.

When we used the definition of an increase in cortisol <9 μg/dL after stimulation of adrenals with 1 μg of Synacthen, the prevalence of relative adrenal insufficiency was 30%. With this definition there was significant difference in cortisol levels, the relative adrenal insufficiency group having lower basal cortisol than those with normal adrenal reserve (median basal cortisol levels 48 μg/dL vs. 115 μg/dL, respectively; $p = .015$) and lower poststimulation increase in cortisol levels (median poststimulation cortisol increase 5.9 vs. 22 μg/dL, respectively; $p = .0001$) (Table 2).

Catecholamine refractory septic shock was more frequent in the relative adrenal insufficiency group compared with the normal adrenal reserve group (five of nine in the adrenal insufficiency group compared with three of 21; $p = .019$).

There were no differences in the two groups (relative adrenal insufficiency vs. no insufficiency) in intravenous fluid requirements, need for mechanical ventilation, or vasoactive drug requirement, except for epinephrine. Six of nine (66.7%) children with relative adrenal insufficiency recovered from septic shock compared with 16 of 21 (76.2%) with normal adrenal reserve ($p = .59$). Five (56%) children with relative adrenal insufficiency died compared with 48% of children with normal adrenal reserve ($p = .69$).

There was a 50% mortality rate in our study subjects. There were no statistically significant differences in the cortisol levels in the two groups by survival (Table 3). Those patients who died had higher median PRISM score (24) compared with survivors (15) ($p = .07$). Duration of ven-

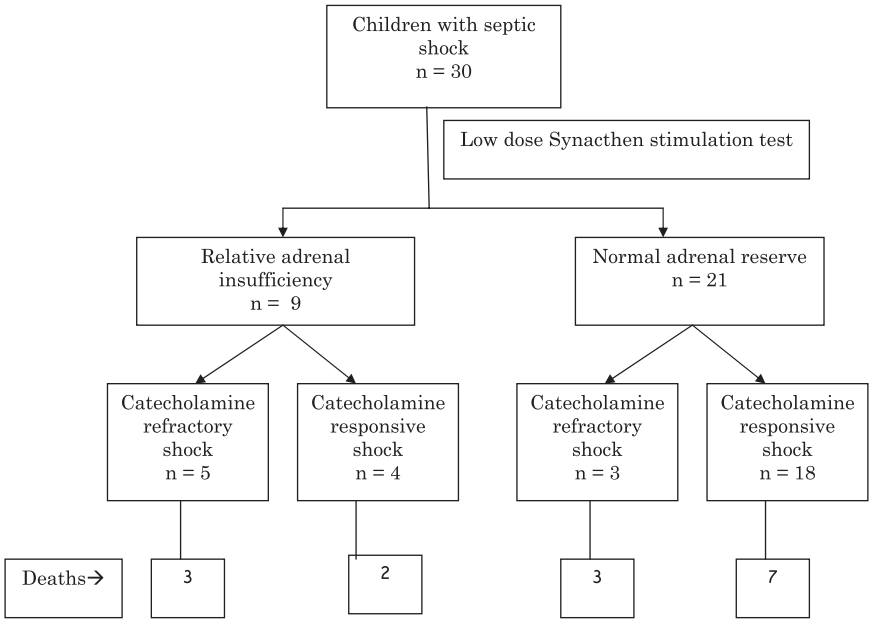

Figure 1. The study profile.

Table 2. Characteristics by adrenal function groups

	Relative Adrenal Insufficiency (After Synacthen Increment in Cortisol <9 μg/dL) (n = 9)	Normal Adrenal Reserve (After Synacthen Increment in Cortisol ≥9 μg/dL) (n = 21)	*p* Value
Age, months, median (95% CI)	60 (6–117.2)	36 (7.9–48)	.229
Boys/girls	6:3	10:11	.338
PRISM score, median (95% CI)	23 (19.16–27.77)	15 (13.45–26.55)	.58
Fluid requirement on day 1, mL/kg, median (95% CI)	140 (120–160)	150 (134.5–166.6)	.55
Catecholamine refractory shock, n (%)	5 (56)	3 (14)	.019
Basal cortisol, μg/dL, median (95% CI)	48 (39.45–67.1)	115 (61.74–157.07)	.015
Cortisol 30 mins after stimulation, μg/dL, median (95% CI)	55 (38.43–72.6)	132.4 (74.47–171.5)	.0019
Cortisol 60 mins after stimulation (μg/dL), median (95% CI)	54 (42.10–68.88)	164 (88.43–224.52)	.0009
Peak increment in cortisol, μg/dL, median (95% CI)	5.9 (2.55–7.98)	22 (13.34–92.77)	<.0001
Deaths, n (%)	5 (56)	10 (48)	.69

CI, confidence interval; PRISM, Pediatric Risk of Mortality.

Table 3. Cortisol values in children with septic shock categorized by outcome

	Survivors (n = 15)	Nonsurvivors (n = 15)	p
Basal cortisol	69 (48.86–81.71)	73 (40.21–121.82)	.52
Cortisol 30 mins after stimulation	76 (57.25–184.5)	80.2 (47.00–153.93)	.44
Cortisol 60 mins after stimulation	96 (56.38–221.68)	84 (44.77–194.08)	.31
Peak increment in cortisol	22 (8.82–62.67)	10.8 (7.79–84.68)	.30
Increment in cortisol at 30 mins	7 (3.34–17.03)	9.2 (0.80–16.03)	.95
Increment in cortisol at 60 mins	22 (7.52–62.66)	10 (4.89–84.64)	.36

Cortisol values given as μg/dL, median (95% confidence interval).

Table 4. Sensitivity and specificity of various cortisol increment cutoffs for development of catecholamine refractory shock

Increment in Cortisol, μg/dL	Increment in Cortisol 30 Mins After Stimulation		Increment in Cortisol 60 Mins After Stimulation		Maximal Cortisol Increase After Stimulation	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
<3	25	81.8	50	95.4	25	100
<4	37.5	77.3	50	95.4	37.5	100
<5	37.5	68.2	62.5	95.4	37.5	100
<6	62.5	68.2	62.5	95.4	62.5	100
<7	62.5	63.6	62.5	90.9	62.5	100
<8	62.5	54.5	75	81.8	62.5	90.9
<9	62.5	50	75	77.3	62.5	81.8
<10	62.5	45.4	75	72.7	62.5	77.3
<11	87.5	40.9	75	68.2	75	72.7
<12	87.5	36.4	87.5	68.2	87.5	72.7
<13	87.5	31.8	87.5	63.6	87.5	63.6
<14	87.5	31.8	87.5	59.1	87.5	63.6
<15	87.5	31.8	87.5	59.1	87.5	59.1

All values are percentages.

tilation was higher in those who died (median duration 105 hrs) compared with survival group (median duration 81 hrs; $p = .04$). Six of the eight children with catecholamine refractory shock died compared with nine of 22 with catecholamine responsive shock ($p = .09$).

Of the eight children with catecholamine refractory shock who received steroids, two children with relative adrenal insufficiency survived compared with none with normal adrenal reserve ($p = .2$). The median (range) epinephrine doses infused in children with catecholamine refractory shock with relative adrenal insufficiency treated with steroids vs. those with adequate reserves treated with steroids were 1.0 (0.5–2) μg/kg/min and 1.5 (0.7–2) μg/kg/min, respectively ($p = .36$). Similarly, there were no significant differences in the amount of fluids infused in these two groups.

The sensitivity and specificity for catecholamine refractory shock with various cutoffs for cortisol (for increment at 30 mins, increment at 60 mins, and the peak increment) were calculated (Table 4, Fig. 2). From this table it appears that the sensitivity and specificity were acceptable at a cutoff of peak increment in cortisol of <6 or 7 μg/dL.

DISCUSSION

We diagnosed relative adrenal insufficiency in 30% of children with fluid refractory septic shock. No child in our study fulfilled criteria for the diagnosis of absolute adrenal insufficiency. Relative adrenal insufficiency was associated with catecholamine refractory shock but not with the outcome.

The major difference from other studies, which used high doses of the synthetic ACTH analogue, was that we used a low dose of synthetic ACTH analogue for stimulation. The stimulus used in the traditional tests is clearly a pharmacologic dose, as this is 100 times greater than the normal stress-induced ACTH level (5). To the best of our knowledge, ours is the first report on adrenal function in children with septic shock that used a more physiologic low-dose (1 μg) stimulation test. However, the criteria for defining adrenal insufficiency with this test are not well defined. For defining relative adrenal insufficiency, we used a cutoff for the increment in cortisol value after stimulation of 9 μg/dL (10, 11). In addition, we calculated the sensitivity and specificity of various cutoff levels for increment in cortisol for the development of catecholamine refractory shock. At a cutoff of <6 or 7 μg/dL, the sensitivity was 62.5% and the specificity 100%. These may be useful cutoffs for defining relative adrenal insufficiency, as children meeting this definition were more likely to have catecholamine refractory shock.

There is no consensus on the definition of adrenal insufficiency in critically ill children. The prevalence of adrenal insufficiency in our patients varies from 0% to 89% according to different definitions used in literature (Table 1). The baseline values were elevated in all our study patients; therefore, according to criteria that use baseline cortisol values, there were no patients in our study who fulfilled the criteria. We do not have a ready explanation for our observation of elevated baseline cortisol levels in children with septic shock in our study; these values were significantly higher than those observed in children with sepsis alone. A recently published study from India reported on the baseline cortisol values in children with meningitis; the mean (SD) serum cortisol was 46.7 (25.1) μg/dL in 16 children with bacterial and 31.9 (15.9) μg/dL in 14 children with aseptic meningitis (22).

It is possible that all our patients had an initial adequate response to the stress induced by septic shock. Thirty percent of these patients had a relative adrenal insufficiency. This suggests that the adrenals may not be able to sustain the enhanced production of cortisol in the presence of persistent shock. This is supported by the observation that children with relative adrenal insufficiency were more likely to develop catecholamine refractory shock. In this context, it may also be interesting to study serial cortisol levels in children with septic shock.

Published reports highlight variations in the incidence of adrenal insufficiency in critically ill children. Hatherill et al. (3) reported a 52% incidence of adrenal insufficiency in 33 children with septic shock; these children had increased requirement of inotropes and vasopressors, but there was no increase in mortality compared with those without adrenal in-

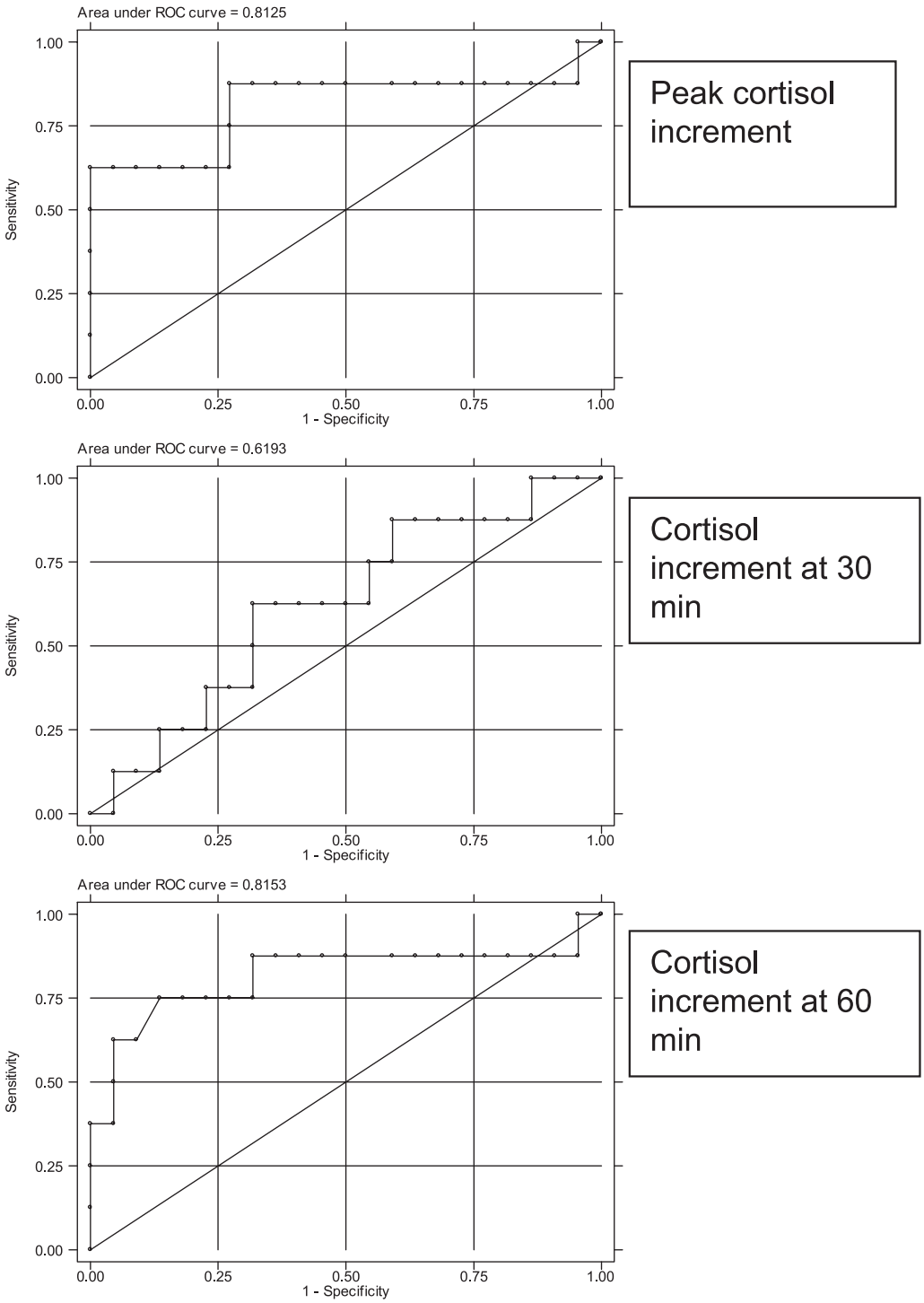

Figure 2. Receiver operating characteristic (*ROC*) curves for prediction of catecholamine refractory shock using various cortical increment cutoffs.

sufficiency. Menon and Clarson (4) reported a 31% incidence of adrenal insufficiency in 13 critically ill children; these children had low basal cortisol levels but mounted an adequate response to external ACTH stimulation. In a recently published study, Pizarro et al. (15) reported an 18% incidence of absolute adrenal insufficiency in 57 children with septic shock and 26% incidence of relative adrenal insufficiency. All three studies used high-dose stimulation tests.

In our study, we excluded children who were at risk for adrenal insufficiency (children who have previously received steroid therapies for chronic illness, and children with abnormal pituitary or adrenal function). The same was done in the earlier studies (4, 15), yet a high incidence of relative adrenal insufficiency was observed in these studies and in our study.

Our observations and those of other authors (4, 15) suggest that adrenal insufficiency is common in children with septic shock, even after excluding children at risk of adrenal insufficiency (children who have previously received steroid therapies for chronic illness, and children with pituitary or adrenal abnormalities),

and these children were more likely to develop catecholamine refractory shock. Pizarro et al. (15) also observed that absolute and relative adrenal insufficiency was absent in children with fluid responsive shock.

The American College of Critical Care Medicine guidelines recommended that hydrocortisone therapy be reserved for use in children with catecholamine resistance and suspected or proven adrenal insufficiency (1). We administered hydrocortisone to children with catecholamine resistance. Of the eight children who had catecholamine refractory shock and received steroids, 40% of those with relative adrenal insufficiency survived compared with none with normal adrenal reserve. Although the difference was not significant, there was a trend toward better outcome (survival) in children with relative adrenal insufficiency and catecholamine refractory shock who received steroids. This suggests that the low-dose Synacthen (1 μg) stimulation test may help to identify a group of patients with catecholamine refractory septic shock who may benefit from steroid therapy. In view of the small sample size, no definite conclusions can be drawn, and a larger and possibly multiple-institution study may be needed to address this issue.

As per the American College of Critical Care Medicine guidelines, when indicated, steroids should be given in the first hour (1). However, the results of cortisol levels may take several hours to get back from the laboratory. In such a situation, steroids could be started in children with catecholamine refractory septic shock after conducting the tests for adrenal function. The results of the tests could then be used to withdraw steroids in the catecholamine-resistant patient if the testing proves the patient to have adequate reserves.

We did not observe any association of relative adrenal insufficiency with mortality. Hatherill et al. (3) and Pizzaro et al. (15) reported the same findings. This suggests that there may be other factors determining mortality, such as multiple organ dysfunction (15).

We did not obtain the cortisol levels at any specific time of the day, as most critically ill patients lose the diurnal variation in their cortisol values (5). The other limitation is a small sample size. We studied the basal cortisol levels only in children with sepsis, and we did not have a control group of healthy children. Use of Synacthen stimulation in children with sepsis and healthy children would have helped us better interpret the elevated cortisol values observed in our study patients.

CONCLUSIONS

Relative adrenal insufficiency is common in children with septic shock and is associated with catecholamine refractory shock; therefore, it may be important to evaluate for this as there is an important clinical implication. Further studies are required to determine the prevalence of adrenal insufficiency in children with septic shock using consensus definitions, especially when using the low-dose stimulation tests, and to determine the benefit of corticosteroid in improving the outcome of children with septic shock.

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