A Prospective Multicenter Study of Adrenal Function in Critically Ill Children

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Abstract

Rationale—Adrenal insufficiency is a clinical condition associated with fluid- and catecholamine-resistant hypotension.

Objectives—The objectives of this study were to determine the prevalence of adrenal insufficiency, risk factors and potential mechanisms for its development, and its association with clinically important outcomes in critically ill children.

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Methods—A prospective, cohort study was conducted from 2005 to 2008 in seven tertiary-care, pediatric intensive care units in Canada on patients up to 17 years of age with existing vascular access. Adrenocorticotrophic hormone stimulation tests (1 µg) were performed and adrenocorticotrophic hormone levels measured in all participants.

Measurements and Main Results—A total of 381 patients had adrenal testing on admission. The prevalence of adrenal insufficiency was 30.2% (95% confidence interval, 25.9–35.1). Patients with adrenal insufficiency had higher baseline cortisol levels (28.6 µg/dl vs. 16.7 µg/dl, $P < 0.001$) and were significantly older (11.5 yr vs. 2.3 yr, $P < 0.001$) than those without adrenal insufficiency. Adrenal insufficiency was associated with an increased need for catecholamines ($P < 0.001$) and more fluid boluses ($P = 0.026$). The sensitivity and specificity of the low-dose adrenocorticotrophic hormone stimulation test were 100% and 84%, respectively.

Conclusions—Adrenal insufficiency occurs in many disease conditions in critically ill children and is associated with an increased use of catecholamines and fluid boluses. It is likely multifactorial in etiology and is associated with high baseline cortisol levels. Further research is necessary to determine which of these critically ill children are truly cortisol deficient before any treatment recommendations can be made.

Keywords

adrenal gland; adrenal function; adrenocorticotrophic hormone

Adrenal insufficiency is a clinical condition associated with hypotension that can be resistant to fluid and catecholamine therapy and, if untreated, can result in increased mortality (1–3). The larger volumes that may need to be given as well as the greater need for catecholamines in patients with unrecognized adrenal insufficiency may result in a longer requirement for mechanical ventilation (4, 5) and a prolonged need for invasive monitoring and vascular access. Adrenal insufficiency may result from dysfunction at the level of the hypothalamus, pituitary, and/or adrenal gland. There has been significant interest in this condition, and the prevalence, definition, mechanisms, and risk factors for its development in children and adults with critical illness have been widely debated since it was first described by Waterhouse and Friderichsen in 1911 (6–12). Two recent randomized controlled trials in adults on the use of steroids in suspected adrenal insufficiency showed conflicting results (12, 13), further adding to the controversy. We identified only a few small observational studies (ranging from 13–72 patients; see Table E1 in the online supplement) examining adrenal insufficiency in pediatric critical illness (14–24).

These pediatric studies used multiple different definitions for the diagnosis of adrenal insufficiency, focused almost exclusively on patients with septic shock (17, 19, 20, 22, 23), did not conduct corticotropin stimulation tests on all patients (only obtained random cortisol levels) (15, 16, 24), and used different doses for the corticotropin tests. As a result, the reported prevalence of adrenal insufficiency varies from 10 (16) to 100% (15). None of the studies identified risk factors for the development of adrenal insufficiency, were adequately powered to assess associations with outcomes, or studied both the high-and low-dose corticotropin tests. Furthermore, the majority of studies did not measure adrenocorticotrophic hormone (ACTH) levels and thus could not comment on possible mechanisms for adrenal

insufficiency in this population. As such there is still no consensus on the diagnosis of or risk factors for the development of adrenal insufficiency in the critically ill pediatric population and the empiric use of corticosteroids is frequent (25), controversial (26), and potentially harmful (27, 28). There is, however, no gold standard for the diagnosis of adrenal insufficiency in critical illness. The 2007 update on clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock (26) recommended hydrocortisone replacement therapy for suspected adrenal insufficiency but did not provide a definition for its diagnosis in pediatric patients. We chose an increment of less than 9 µg/dl as our definition as it is currently the one most commonly accepted by critical care physicians and experts in the field (12, 13, 17, 19–21).

The objectives of this study were to prospectively determine the prevalence of adrenal insufficiency, risk factors and mechanisms for its development, and its association with clinically important outcomes using the low- and high-dose ACTH stimulation tests in critically ill children. Some of the results of this study have been previously reported in the form of an abstract (29).

METHODS

Patients and Sites

We conducted a prospective, multicenter study in seven tertiary care pediatric intensive care units (PICUs) in Canada. Patients were eligible if they were newborn to 17 years of age, had arterial or central venous catheters, and were enrolled within 24 hours of admission. We excluded premature infants and patients with known or suspected adrenal, pituitary, or hypothalamic disease. We also excluded those who received systemic steroids for more than 10 days in the previous month or had more than one dose of systemic steroids within the 24 hours before admission (except dexamethasone) and those who were expected to have care withdrawn or were transferred from another ICU. None of the patients received etomidate. The study was approved by the research ethics board at each participating center. Written informed consent was obtained for all study participants.

Study Protocol

Patients had a random cortisol, ACTH, glucose, and electrolyte levels measured after enrollment. Patients were given 1 µg of Cosyntropin (Cortrosyn, Scarborough, ON, Canada) intravenously with a repeat cortisol level measured at 30 minutes (16, 30). Patients who were still in the PICU and had vascular access on the second day of PICU admission had low-dose testing as above followed by high-dose ACTH (31, 32) (15 µg/kg for those <2 yr old; 250 µg for those >2 yr old) given at 60 minutes after low-dose ACTH (32–35). A post-ACTH cortisol level was measured 1 hour after administration of the high-dose ACTH. After centrifugation, serum samples were stored at –20°C and sent to a central laboratory for analysis. Plasma cortisol levels were measured using the Elecsys cortisol assay (Roche Diagnostics, Indianapolis, IN) and serum ACTH was measured by radioimmunoassay (ACTH IRMA; Stillwater, MN). We documented baseline characteristics, including diagnosis, age, the Pediatric Risk of Mortality Score (PRISM III) (36) and the Pediatric Logistic Organ Dysfunction (PELOD) Score (37) on all patients.

Outcomes Measures

The primary objective for this study was to determine the prevalence of adrenal insufficiency on the day of admission to the PICU. Secondary objectives were to identify possible risk factors for adrenal insufficiency, including age, diagnoses, and illness severity; to determine the association of adrenal insufficiency with the need for catecholamines (adrenaline, noradrenaline, or dopamine), fluid boluses (colloids and crystalloids that were given outside of maintenance fluids and medications), and PICU mortality; and to determine the sensitivity and specificity of the low-dose as compared with the high-dose ACTH test.

Sample Size and Statistical Analysis

Based on quoted estimates in the literature (14, 16–18, 20–23), we assumed a prevalence of 40%; therefore, a sample size of 369 patients permitted an estimate of prevalence to within $\pm 5\%$, 19 times out of 20. To allow for a potential dropout rate of 5%, the total sample size was 389.

Descriptive statistics were used to summarize the study sample. The prevalence of adrenal insufficiency on both Day 1 and Day 2 was calculated with Wilson score continuity correction used for the 95% confidence interval (CI) (38). The association between adrenal insufficiency and baseline characteristics, potential risk factors, and clinically important secondary outcomes was tested using Fisher exact test for dichotomous variables and Mann-Whitney test for continuous variables. Length of stay in the PICU was compared between the two study groups using a time-to-event approach (Breslow test). A logistic regression model using age, PRISM, and PELOD scores as potential confounders was used to assess the relationship between different diagnostic categories and adrenal insufficiency. Sensitivity analyses using the other definitions of adrenal insufficiency in the literature were conducted for the association of the prevalence of adrenal insufficiency and the need for catecholamines, fluid boluses, and mortality. A *P* value of less than 0.05 was considered significant. The sensitivity and specificity of the low-dose ACTH test were also determined.

RESULTS

Study Participants

From June 2005 to July 2008, a total of 4,090 patients were admitted to the seven participating PICUs. Eligibility criteria were met by 1,707 patients (22.4%). Of those excluded, 415 (17.4%) patients had received more than one dose of steroids within the previous 24 hours (the reasons for steroid use were not recorded) and 5.8% of excluded patients had had more than 10 days of systemic steroids in the previous month. Of the 1,707 eligible patients, 438 (25.7%) could not be give consent within 24 hours of admission to the PICU, 528 had parents or guardians who declined consent, and 389 patients (23%) were enrolled. There was no difference in the PRISM scores (6 [interquartile range {IQR} 3–10] vs. 6 [IQR 3–9]; *P* = 0.81) or ages (*P* = 0.72) of those in whom consent was and was not obtained. Five patients (1.2%) did not complete Day 1 testing, and data were incomplete in three patients (1.2%), resulting in 381 patients (22.3%) being analyzed for Day 1. On Day 2, 205 patients (52.7%) were still in the PICU and therefore met criteria for Day 2 testing; 3 patients (1.5%) had incomplete data resulting in 202 patients (51.9%) being analyzed using

the low-dose ACTH test alone and 200 patients for the sequential low-and high-dose ACTH testing.

Baseline and Day 1 characteristics of the patients enrolled in the study are presented in Table 1. The overall patient cohort had a median age of 4.01 years (IQR, 0.56–12.98), were 50.6% male, and on admission had a median PRISM score of 6 (IQR, 3–10) and a median PELOD score of 11 (IQR, 1–12). A total of 197 patients (67.4%) were mechanically ventilated at the time of enrollment. Fifteen percent of patients enrolled had been on steroids (oral, inhaled, or intravenous) within the preceding month.

Prevalence

On the day of admission, 115 patients (30.2%; 95% CI, 25.9–35.1%) had adrenal insufficiency as defined by an increment in cortisol less than 9 µg/dl using the low-dose ACTH test. Of the 202 patients tested on Day 2, 40 (19.8%; 95% CI, 14.9–25.8%) had adrenal insufficiency (Table E2). The prevalence of adrenal insufficiency by other definitions in the literature varied from 4.5 to 41.9% on Day 1 and 4.4 to 31.7% on Day 2. The prevalence of adrenal insufficiency was 62.5% (95% CI, 38.6–81.5%) in trauma patients, 32.8% (95% CI, 22.1–45.6%) in septic patients, 19.3% (95% CI, 13.8–26.4%) in cardiac surgical patients, and 29.3% (95% CI, 24.3–35.0%) in surgical patients as a whole. The relative risk of developing adrenal insufficiency in patients with different diagnoses is provided in Table E3.

Serum Cortisol and ACTH Levels

The baseline cortisol and corresponding ACTH levels in patients with adrenal insufficiency are shown in Table 2. One hundred thirteen patients with adrenal insufficiency had ACTH levels tested. Ten (8.7%) of the adrenally insufficient patients had baseline cortisol levels greater than 36 µg/dl and high ACTH levels. Almost 17% (19/113) of patients had very low baseline cortisol levels (<18 µg/dl) and inappropriately normal ACTH levels. The distribution of serum cortisol levels pre and post ACTH stimulation as well as the range of responses to ACTH in the whole cohort is provided in Figure E1.

Risk Factors and Clinically Important Outcomes

Increasing age was associated with a higher prevalence of adrenal insufficiency on both Day 1 and Day 2. Each additional year of age increased the odds of adrenal insufficiency on average by 11% ($P < 0.001$) (Table E4). In a regression analysis, adjusted for age, PRISM, and PELOD scores, the odds ratio of adrenal insufficiency was increased with a diagnosis of trauma (1.77; 95% CI, 1.01–8.66). Surgery as a whole ($P = 0.62$), illness severity as measured by PRISM ($P = 0.52$) and PELOD ($P = 0.33$) scores, and duration of mechanical ventilation ($P = 0.65$) were not found to be associated with an increased risk of adrenal insufficiency. Cardiac surgery ($P < 0.001$) was associated with a decreased risk of adrenal insufficiency. Thirty-seven of 150 (24.7%) cardiac surgery patients received a single dose of high-dose methylprednisolone between 20 and 24 hours before enrollment.

Patients who had adrenal insufficiency on Days 1 and 2 had similar PRISM scores on Day 1 (7.0 vs. 6.5, $P = 0.18$) but were on a higher mean number of catecholamines (0.5 ± 0.6 vs.

0.9 $\pm$ 0.7; $P=0.01$) when compared with those with adrenal insufficiency on Day 1 alone. Sixty-five of 202 patients tested on both days had adrenal insufficiency on Day 1; adrenal insufficiency was no longer present on Day 2 in 40 of these patients. Figure E2 shows the distribution of baseline cortisol levels in patients in whom adrenal insufficiency did and did not resolve. Use of steroids in the previous 6 months by any route was not statistically associated with an increased risk of adrenal insufficiency ($P=0.54$). There was no significant difference in the number of patients who received steroids after enrollment into the study between those with and without adrenal insufficiency (8/115 vs. 12/266; $P=0.33$).

Adrenal insufficiency on Day 1 of admission was associated with the need for a greater number of catecholamines ($P<0.001$), greater number of days on catecholamines ($P=0.002$), and more fluid boluses ($P=0.03$), as shown in Table 3. The PICU mortality rate in the whole cohort was 1.3% (5/381) with four patients being in the adrenal insufficiency group ($P=0.03$). Adrenal insufficiency by other definitions in the literature, including low random cortisol levels, was not associated with an increased need for catecholamines or fluid (see Table 4).

Low- Versus High-Dose Testing

The low-dose test had a sensitivity of 1.00 and specificity of 0.84 (Table 5). The positive predictive value and negative predictive value were 23 and 100%, respectively, and the positive likelihood ratio for the low-dose test was 6.25. Of the 39 patients with an increment of less than 9 $\mu\text{g/dl}$ using the low-dose testing, 9 patients had a peak cortisol level less than 18 $\mu\text{g/dl}$. No patients had a peak cortisol level less than 18 $\mu\text{g/dl}$ using the high-dose testing.

DISCUSSION

In this large, prospective, multicenter study we found that adrenal insufficiency, as defined by an increment in cortisol level less than 9 $\mu\text{g/dl}$, was present in many disease conditions and was more common with increasing age. Despite the longstanding focus in the literature on adrenal function in sepsis (17, 19, 20, 22, 23), in our study the presence of sepsis was not associated with an increased risk of adrenal insufficiency. Adrenal insufficiency was associated with an increased use of catecholamines and increased volume of fluid boluses.

Although a significant proportion of our patient population had a surgical diagnosis, surgery was not an independent risk factor for the development of adrenal insufficiency. Cardiac surgery patients appeared to have a significantly decreased incidence of adrenal insufficiency on Day 1 and Day 2, suggesting that a single large dose of steroids does not result in adrenal suppression.

Our study suggests that the mechanisms for adrenal dysfunction in critically ill children may be highly variable and multifactorial. In the majority of patients with adrenal insufficiency, the baseline cortisol level was greater than 18 $\mu\text{g/dl}$ but did not increase with exogenous ACTH stimulation; this lack of increase was associated with clinically important outcomes in this study and in those by Sarthi and colleagues (20) and Hatherill and colleagues (23). It is not clear if this is because the ability of the adrenal gland to mount an adequate response

despite a normal baseline during critical illness is important or because this definition of adrenal insufficiency is simply a marker of the need for catecholamines and fluid or a reflection of end-organ resistance (9, 39) in critically ill patients. Although patients with baseline cortisol levels greater than 36 µg/dl may still have dysfunction of the hypothalamic-pituitary-adrenal axis, they may not respond to exogenous glucocorticoids as the plasma cortisol levels achieved by 1 to 2 mg/kg of hydrocortisone administration may not be significantly higher than those already present in these patients (40). This may partially explain the negative result seen in some intervention trials in which patients had higher mean baseline cortisol levels (12) versus a positive result in others with lower mean baseline cortisol levels (13).

The prevalence of adrenal insufficiency using the low-dose ACTH test on Day 2 was 19.5% and using the high-dose test was 4.5%. The high-dose test did not identify any patients who were not identified by the low-dose test. Almost half of our total patient cohort had baseline cortisol levels less than 18 µg/dl and inappropriately normal ACTH levels suggestive of hypothalamic-pituitary-adrenal axis dysfunction; therefore, use of the high-dose ACTH test may result in underdiagnosis of adrenal insufficiency in this patient population (41). Furthermore, the high-dose test would not have identified any patients with adrenal insufficiency using the definition often used by endocrinologists (25) (peak cortisol level < 18 µg/dl). Finally, the low-dose ACTH test identified nine patients with an increment in cortisol of less than 9 µg/dl as well as a peak cortisol level less than 18 µg/dl who were not identified by high-dose testing. This is important because such patients may require longer-term endocrinology follow-up. Only 38% of patients tested on both days still had adrenal insufficiency on Day 2, suggesting that adrenal insufficiency in some critically ill children may be temporary, thus raising questions about the necessity of replacement steroids in these patients. There are no large randomized controlled trials on the use of steroids in critically ill children, yet many intensivists report using steroids to treat catecholamine- and fluid-resistant shock (25), and steroids have been recommended in guidelines for the treatment of catecholamine-resistant shock in children (26).

This study has many strengths. It is the only critical care trial to examine the prevalence of adrenal insufficiency in a wide spectrum of critically ill patients. Furthermore, it is the only study to explore potential mechanisms of adrenal insufficiency in the critically ill pediatric population using sequential low- and high-dose ACTH testing as well as the measurement of ACTH levels. A potential limitation of this study is that some of the sicker septic patients may have been excluded because they were started on steroids for fluid- and catecholamine-resistant shock. The patients with sepsis in our cohort had a median PRISM score of 7 (IQR 5–13), a 79.3% mechanical ventilation rate, and 57.6% were on catecholamines suggesting that we recruited a relatively ill septic population. Another potential limitation of this study is that it did not measure free cortisol levels (42, 43); however, the increment in cortisol level is independent of serum protein levels and free cortisol measurements are only available in research laboratories, thereby limiting their clinical usefulness. Finally, this study only included those patients with existing vascular access and likely represents the more critically ill patients within the PICU population; however, the significance of this is unclear as illness severity was not found to be associated with adrenal insufficiency in this or other studies (16, 17).

In summary, adrenal insufficiency, as currently defined in the critical care literature, occurs in a wide spectrum of disease conditions in critically ill children and is associated with an increased need for catecholamines and fluid. Adrenal insufficiency is likely multifactorial in etiology and is associated with high baseline cortisol levels. Further research is necessary to determine which of these critically ill children are truly cortisol deficient before any treatment recommendations can be made.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Bouachour G, Tirot P, Varache N, Gouello JP, Harry P, Alquier P. Hemodynamic changes in acute adrenal insufficiency. *Intensive Care Med.* 1994; 20:138–141. [PubMed: 8201094]
2. Hinshaw LB, Beller BK, Chang AC, Murray CK, Flournoy DJ, Passey RB, Archer LT. Corticosteroid/antibiotic treatment of adrenalectomized dogs challenged with lethal *E. coli*. *Circ Shock.* 1985; 16:265–277. [PubMed: 3902272]
3. Ledingham IM, Watt I. Influence of sedation on mortality in critically ill multiple trauma patients. *Lancet.* 1983; 1:1270.
4. Prakanrattana U, Valairucha S, Sriyoschati S, Pornvilawan S, Phanchaipetch T. Early extubation following open heart surgery in pediatric patients with congenital heart diseases. *J Med Assoc Thai.* 1997; 80:87–95. [PubMed: 9078692]
5. Huang CJ, Lin HC. Association between adrenal insufficiency and ventilator weaning. *Am J Respir Crit Care Med.* 2006; 173:276–280. [PubMed: 16272449]
6. Beishuizen A, Thijs LG. Relative adrenal failure in intensive care: an identifiable problem requiring treatment? *Best Pract Res Clin Endocrinol Metab.* 2001; 15:513–531. [PubMed: 11800521]
7. Cooper MS, Stewart PM. Corticosteroid insufficiency in acutely ill patients. *N Engl J Med.* 2003; 348:727–734. [PubMed: 12594318]
8. Cronin L, Cook DJ, Carlet J, Heyland DK, King D, Lansang MA, Fisher CJ Jr. Corticosteroid treatment for sepsis: a critical appraisal and meta-analysis of the literature. *Crit Care Med.* 1995; 23:1430–1439. [PubMed: 7634816]
9. Marik PE, Zaloga GP. Adrenal insufficiency in the critically ill: a new look at an old problem. *Chest.* 2002; 122:1784–1796. [PubMed: 12426284]
10. Lefering R, Neugebauer EA. Steroid controversy in sepsis and septic shock: a meta-analysis. *Crit Care Med.* 1995; 23:1294–1303. [PubMed: 7600840]
11. 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. [PubMed: 15289273]
12. Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K, Weiss YG, Benbenishty J, Kalenka A, Forst H, et al. Hydrocortisone therapy for patients with septic shock. *N Engl J Med.* 2008; 358:111–124. [PubMed: 18184957]
13. Annane D, Seville V, Charpentier C, Bollaert PE, Francois B, Korach JM, Capellier G, Cohen Y, Azoulay E, Troche G, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA.* 2002; 288:862–871. [PubMed: 12186604]

14. Hebbar K, Rigby MR, Felner EI, Easley KA, Fortenberry JD. Neuroendocrine dysfunction in pediatric critical illness. *Pediatr Crit Care Med*. 2009; 10:35–40. [PubMed: 19057442]
15. Ando M, Park IS, Wada N, Takahashi Y. Steroid supplementation: a legitimate pharmacotherapy after neonatal open heart surgery. *Ann Thorac Surg*. 2005; 80:1672–1678. [PubMed: 16242437]
16. 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; 110:563–569. [PubMed: 12205261]
17. Casartelli CH, Garcia PC, Branco RG, Piva JP, Einloft PR, Tasker RC. Adrenal response in children with septic shock. *Intensive Care Med*. 2007; 33:1609–1613. [PubMed: 17541546]
18. Menon K, Clarson C. Adrenal function in pediatric critical illness. *Pediatr Crit Care Med*. 2002; 3:112–116. [PubMed: 12780978]
19. Pizarro CF, Troster EJ, Damiani D, Carcillo JA. Absolute and relative adrenal insufficiency in children with septic shock. *Crit Care Med*. 2005; 33:855–859. [PubMed: 15818116]
20. Sarthi M, Lodha R, Vivekanandhan S, Arora NK. 2006 Adrenal status in children with septic shock using low-dose stimulation test. *Pediatr Crit Care Med*. 2007; 8:23–28. [PubMed: 17251878]
21. Samransamruajkit R, Jitchaiwat S, Deerojanawong J, Sritippayawan S, Praphal N. Adrenal insufficiency in early phase of pediatric acute lung injury/acute respiratory distress syndrome. *J Crit Care*. 2007; 22:314–318. [PubMed: 18086402]
22. Riordan FA, Thomson AP, Ratcliffe JM, Sills JA, Diver MJ, Hart CA. Admission cortisol and adrenocorticotrophic hormone levels in children with meningococcal disease: evidence of adrenal insufficiency? *Crit Care Med*. 1999; 27:2257–2261. [PubMed: 10548217]
23. Hatherill M, Tibby SM, Hilliard T, Turner C, Murdoch IA. Adrenal insufficiency in septic shock. *Arch Dis Child*. 1999; 80:51–55. [PubMed: 10325759]
24. Gajarski RJ, Stefanelli CB, Graziano JN, Kaciroti N, Charpie JR, Vazquez D. Adrenocortical response in infants undergoing cardiac surgery with cardiopulmonary bypass and circulatory arrest. *Pediatr Crit Care Med*. 2010; 11:44–51. [PubMed: 19451847]
25. Menon K, Lawson M. Identification of adrenal insufficiency in pediatric critical illness. *Pediatr Crit Care Med*. 2007; 8:276–278. [PubMed: 17417118]
26. Brierley J, Carcillo JA, Choong K, Cornell T, Decaen A, Deymann A, Doctor A, Davis A, Duff J, Dugas MA, et al. Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. *Crit Care Med*. 2009; 37:666–688. [PubMed: 19325359]
27. Tabarki B, Coffinieres A, Van Den BP, Huault G, Landrieu P, Sebire G. Critical illness neuromuscular disease: clinical, electrophysiological, and prognostic aspects. *Arch Dis Child*. 2002; 86:103–107. [PubMed: 11827903]
28. Markovitz BP, Goodman DM, Watson RS, Bertoch D, Zimmerman J. A retrospective cohort study of prognostic factors associated with outcome in pediatric severe sepsis: what is the role of steroids? *Pediatr Crit Care Med*. 2005; 6:270–274. [PubMed: 15857523]
29. Menon, K. Final results of the adrenal insufficiency study in pediatric critical illness. Presented at the Canadian Critical Care Forum; October 25, 2009; Toronto, Canada.
30. Rose SR, Lustig RH, Burstein S, Pitukcheewanont P, Broome DC, Burghen GA. Diagnosis of ACTH deficiency. Comparison of overnight metyrapone test to either low-dose or high-dose ACTH test. *Horm Res*. 1999; 52:73–79. [PubMed: 10681636]
31. Marik PE, Kiminyo K, Zaloga GP. Adrenal insufficiency in critically ill patients with human immunodeficiency virus. *Crit Care Med*. 2002; 30:1267–1273. [PubMed: 12072680]
32. Marik PE, Zaloga GP. Adrenal insufficiency during septic shock. *Crit Care Med*. 2003; 31:141–145. [PubMed: 12545007]
33. Park YJ, Park KS, Kim JH, Shin CS, Kim SY, Lee HK. Reproducibility of the cortisol response to stimulation with the low dose (1 microg) of ACTH. *Clin Endocrinol (Oxf)*. 1999; 51:153–158. [PubMed: 10468984]
34. Huang TS, Jiang YD. Repetitive graded ACTH stimulation test for adrenal insufficiency. *J Endocrinol Invest*. 2000; 23:163–169. [PubMed: 10803473]
35. Crowley S, Hindmarsh PC, Honour JW, Brook CG. Reproducibility of the cortisol response to stimulation with a low dose of ACTH(1–24): the effect of basal cortisol levels and comparison of

- low-dose with high-dose secretory dynamics. *J Endocrinol.* 1993; 136:167–172. [PubMed: 8429271]
36. Pollack MM, Patel KM, Ruttimann UE. PRISM III: an updated Pediatric Risk of Mortality score. *Crit Care Med.* 1996; 24:743–752. [PubMed: 8706448]
37. Leteurtre S, Martinot A, Duhamel A, Proulx F, Grandbastien B, Cotting J, Gottesman R, Joffe A, Pfenninger J, Hubert P, et al. Validation of the Paediatric Logistic Organ Dysfunction (PELOD) score: prospective, observational, multicentre study. *Lancet.* 2003; 362:192–197. [PubMed: 12885479]
38. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. *Stat Med.* 1998; 17:857–872. [PubMed: 9595616]
39. Cooper MS, Stewart PM. Adrenal insufficiency in critical illness. *J Intensive Care Med.* 2007; 22:348–362. [PubMed: 18048877]
40. Sainsbury JR, Stoddart JC, Watson MJ. Plasma cortisol levels. A comparison between sick patients and volunteers given intravenous cortisol. *Anaesthesia.* 1981; 36:16–21. [PubMed: 7468958]
41. Dimopoulou I, Ilias I, Roussou P, Gavala A, Malefaki A, Milou E, Pitaridis M, Roussos C. Adrenal function in non-septic long-stay critically ill patients: evaluation with the low-dose (1 µg) corticotropin stimulation test. *Intensive Care Med.* 2002; 28:1168–1171. [PubMed: 12185444]
42. Hamrahian AH, Oseni TS, Arafah BM. Measurements of serum free cortisol in critically ill patients. *N Engl J Med.* 2004; 350:1629–1638. [PubMed: 15084695]
43. Poomthavorn P, Lertbunrion R, Preutthipan A, Sriphrapadang A, Khlairit P, Mahachoklertwattana P. Serum free cortisol index, free cortisol, and total cortisol in critically ill children. *Intensive Care Med.* 2009; 35:1281–1285. [PubMed: 19352620]

AT A GLANCE COMMENTARY**Scientific Knowledge on the Subject**

Adrenal insufficiency is characterized by hypotension that may be resistant to fluid and catecholamine therapy. Although there has been significant interest in this condition over the years, the prevalence, definition, mechanisms, and risk factors for its development in critical illness remain unclear.

What This Study Adds to the Field

This study found that the prevalence of adrenal insufficiency in critically ill children is 30%, is associated with increased fluid and catecholamine requirements, and is likely multifactorial in etiology.

TABLE 1

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF STUDY POPULATION

Characteristic	All Patients (n = 389)	AI (n = 115)	No AI (n = 266)	P Value
Age, yr, median (IQR)	4.01 (0.56–13.0)	11.5 (3.3–15.5)	2.3 (0.5–11.2)	< 0.001
Weight, kg, median (IQR)	16.25 (7.40–41.0)	30 (15.6–58.3)	12.3 (6.3–33.4)	<0.001
Male sex, no. (%)	198 (50.9)	57 (49.6)	135 (51.1)	0.91
PRISM score, median (IQR)	6 (3–10)	6 (3–10)	5.5 (3–9)	0.52
PELOD score, median (IQR)	11 (1–12)	11 (1–12)	11 (1–12)	0.33
Mechanical ventilation, no. (%)	263 (67.6)	84 (73.0)	178 (67.4)	0.33
Receiving catecholamines, no. (%)	111 (28.5)	47 (40.9)	62 (23.3)	0.001
Glucose, mmol/L, median (IQR)	6.4 (5.4–7.5)	6.3 (5.2–7.4)	6.5 (5.5–7.6)	0.22
Basal cortisol, µg/dl, median (IQR)	20 (10.4–34.3)	28.6 (19.8–43.5)	16.7 (8.0–29.4)	<0.001
Diagnosis no. (%)				
All trauma	14 (3.6)	10 (8.7)	6 (2.3)	0.01
Head trauma	9 (2.3)	4 (3.5)	4 (1.5)	0.250
Sepsis	59 (15.2)	19 (16.5)	39 (14.7)	0.64
Surgical	282 (72.5)	81 (70.4)	195 (73.3)	0.62
Cardiac surgery	152 (39.1)	29 (25.2)	121 (45.5)	<0.001

Definition of abbreviations: ACTH = adrenocorticotrophic hormone; AI = adrenal insufficiency; IQR = interquartile range; PELOD = Pediatric Logistic Organ Dysfunction; PRISM = Pediatric Risk of Mortality.

There were 389 patients in the cohort, of whom 381 patients were included in the final analysis. Measurements are from Day 1.

TABLE 2**CORTISOL AND ADRENOCORTICOTROPIC HORMONE LEVELS OF PATIENTS WITH ADRENAL INSUFFICIENCY**

ACTH	Cortisol		
	<18.0 µg/dl	18.1–36.0 µg/dl	>36.0 µg/dl
Low (<5.9 pg/ml)	1	1	0
Normal	18	39	32
High (>56.8 pg/ml)	1	11	10

Definition of abbreviation: ACTH = adrenocorticotrophic hormone.

ACTH testing was completed in 113/115 patients with adrenal insufficiency on Day 1.

TABLE 3**CLINICAL OUTCOMES FOR THOSE WITH AND WITHOUT ADRENAL INSUFFICIENCY ON DAY 1**

Clinical Outcome	AI (n = 115)	No AI (n = 266)	P Value
Days on catecholamines	0.97 ± 1.50	0.68 ± 1.58	0.002
Number of catecholamines	0.47 ± 0.65	0.24 ± 0.49	<0.001
Catecholamines at any time, no. (%)	47 (40.9)	62 (23.3)	0.001
Fluid boluses, ml/kg/24 h	8.33 (0.00–25.73)	2.27 (0.00–16.06)	0.03
Received fluid boluses, no. (%)	70 (60.9)	133 (50)	0.06
Days on mechanical ventilation	2 (1–5.8)	2 (1–5)	0.65
PICU length of stay, d	4 (2,7)	4 (2,6)	0.88
PICU mortality, no. (%)	4 (3.5)	1 (0.4)	0.03

Definition of abbreviations: AI = adrenal insufficiency (increment in cortisol <9 µg/dl); PICU = pediatric intensive care unit.

Total fluid intake, days on mechanical ventilation, and PICU length of stay are presented as median values (interquartile range).

TABLE 4

ASSOCIATION OF ADRENAL INSUFFICIENCY WITH OUTCOME USING OTHER DEFINITIONS

Definition of AI, µg/dl Cortisol	AI	No AI	P Value
Baseline <5, no.	52	330	
Days on catecholamines	0.15 ± 0.64	0.86 ± 1.64	<0.001
No. of catecholamines	0.08 ± 0.27	0.35 ± 0.58	0.001
Fluid boluses, ml/kg/24 h	0.0 (0.00–6.70)	0.0 (0.00–9.62)	0.67
Peak <18, no.	42	341	
Days on catecholamines	0.64 ± 1.46	0.78 ± 1.57	0.49
No. of catecholamines	0.26 ± 0.54	0.31 ± 0.56	0.49
Fluid boluses, ml/kg/24 h	5.98 (0.00–21.97)	5.06 (0.00–20.0)	0.96
Baseline <5 or peak <18 or increment <9, no.	163	219	
Days on catecholamines	0.74 ± 1.38	0.79 ± 1.68	0.57
No. of catecholamines	0.35 ± 0.59	0.28 ± 0.52	0.27
Fluid boluses, ml/kg/24 h	4.81 (0.00–20.0)	7.69 (0.00–20.37)	0.82
Baseline and peak <18 and increment <9, no.	17	365	
Days on catecholamines	0.71 ± 0.99	0.77 ± 1.58	0.41
No. of catecholamines	0.47 ± 0.72	0.30 ± 0.55	0.32
Fluid boluses, ml/kg/24 h	15.63 (0.00–28.77)	5.0 (0.00–19.88)	0.22
Baseline <276 or increment <250, no.	195	186	
Days on catecholamines	0.73 ± 1.41	0.81 ± 1.71	0.927
No. of catecholamines	0.33 ± 0.58	0.29 ± 0.53	0.611
Fluid boluses, ml/kg/24 h	4.61 (0.00–20.00)	8.40 (0.00–20.38)	0.729

Definition of abbreviation: AI = adrenal insufficiency; PICU = pediatric intensive care unit.

Number of days on catecholamines, fluid boluses, days on mechanical ventilation and PICU length of stay are presented as median values (interquartile range). Plus-minus values are means ± SD. Numbers for each definition were derived by using all the patients who had data available for that definition.

TABLE 5**SENSITIVITY TESTING OF THE LOW-DOSE ADRENOCORTICOTROPIC HORMONE TEST**

	High-Dose Positive	High-Dose Negative	Total
Low-dose positive	9	30	39
Low-dose negative	0	161	161
Total	9	191	200

Definition of abbreviation: ACTH = adrenocorticotrophic hormone.

High-dose test on Day 2 was used as the gold standard.