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Hydrocortisone Therapy in Catecholamine Resistant Pediatric Septic Shock: A Pragmatic Analysis of Clinician Practice and Association with Outcomes

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Abstract

Purpose—The 2012 Surviving Sepsis Campaign pediatric guidelines recommend stress dose hydrocortisone (SDH) in children experiencing catecholamine dependent septic shock with suspected or proven absolute adrenal insufficiency. We evaluated whether SDH therapy in children with catecholamine dependent septic shock correlated with random serum total cortisol (rSTC) levels and was associated with improved outcomes.

Methods—With IRB approval, we retrospectively enrolled consecutive children (1 month to 18 years old) admitted to the pediatric intensive care unit (PICU) from January 1, 2013 to December 31, 2013 with catecholamine dependent septic shock who had rSTC levels measured prior to potential SDH therapy. The cohort was dichotomized to rSTC < 18 mcg/dL and ≥ 18 mcg/dL. Associations of SDH with outcomes: PICU mortality, PICU and hospital length of stay (LOS), ventilator free days (VFD) and vasopressor free days (VPFD) were examined.

Results—Seventy children with catecholamine dependent septic shock and measured rSTC levels were eligible (16% PICU mortality). While 43% (30/70) had rSTC < 18 mcg/dL, 60% (42/70) received SDH. Children with rSTC < 18 mcg/dL had lower severity of illness and lower vasopressor-inotrope scores than those with rSTC ≥ 18 mcg/dL (all $p < 0.05$). Children with SDH

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had higher severity of illness and PICU mortality than those without SDH (all $p<0.05$). Mean rSTC levels were similar in children with and without SDH (21.1 vs. 18.7 mcg/dL, $p=0.69$). In children with rSTC < 18 mcg/dL, SDH was associated with greater PICU and hospital LOS, and fewer VFD (all $p<0.05$). In children with rSTC > 18 mcg/dL, SDH was associated with greater PICU mortality, and fewer VFD and VPFD (all $p<0.05$).

Conclusions—SDH therapy in children with catecholamine dependent septic shock correlated more with severity of illness than rSTC levels and was associated with worse outcomes, irrespective of rSTC levels.

Keywords

hydrocortisone; septic shock; cortisol; critical illness; pediatrics

Introduction

Severe sepsis and septic shock are leading causes of morbidity and mortality in children (1–4). The role of stress dose hydrocortisone (SDH) therapy in this setting to reverse shock associated with suspected or proven adrenal insufficiency continues to be a subject of considerable investigation. Guidelines from the Surviving Sepsis Campaign in 2012 recommend timely SDH therapy in children experiencing fluid refractory catecholamine dependent septic shock with suspected or proven absolute adrenal insufficiency (Grade 1A – strong recommendation based on high quality evidence) (5). While the pediatric sub-group guidelines do not explicitly define a threshold random serum total cortisol (rSTC) level to prescribe SDH therapy, indications for pediatric therapy are typically extrapolated from the adult guidelines that state that “an inappropriately low rSTC level < 18 mcg/dL in a patient with shock would be considered an indication for steroid therapy along traditional adrenal insufficiency guidelines” (5,6).

Although the pathophysiological changes in severe sepsis with fluid refractory catecholamine dependent septic shock with suspected or proven absolute adrenal insufficiency provide biological plausibility for benefit from therapy with SDH (7–9), clinical studies of SDH therapy to improve outcomes in both adults and children being managed for septic shock with suspected or proven absolute adrenal insufficiency have demonstrated equivocal results (10–15). Additionally, clinician surveys of attitudes and practice regarding SDH therapy in the setting of catecholamine dependent pediatric septic shock with suspected or proven absolute adrenal insufficiency demonstrate wide variations in criteria for diagnosis of adrenal insufficiency and indications for therapy with SDH (16–18). It is unclear whether the guideline specified rSTC cut-off of 18 mcg/dL is a pragmatic threshold for SDH therapy in catecholamine dependent pediatric septic shock with suspected or proven absolute adrenal insufficiency, and if SDH therapy based on this rSTC level is associated with improved outcomes.

The primary objective of our study was to evaluate the association of guideline based SDH therapy in critically ill children experiencing fluid refractory catecholamine dependent septic shock with clinical outcomes. Our secondary objective was to examine the correlations between SDH therapy, rSTC levels and severity of illness.

Materials and Methods

Study Design and Patient Selection

We performed a retrospective chart review study of critically ill children aged 1 month to 18 years consecutively admitted to the pediatric intensive care unit (PICU) at The Children's Hospital of Philadelphia between January 1, 2013 and December 31, 2013. The PICU is a non-cardiac medical-surgical unit with a capacity of 55 beds and annual volume of approximately 3600 admissions. Critically ill children with catecholamine dependent septic shock and rSTC levels measured prior to potential SDH therapy were included in this study. We excluded children with corrected gestational age < 44 weeks, history of cardiac surgery within the preceding six months, and SDH administration prior to obtaining rSTC level. This study was approved by the Institutional Review Board for the Protection of Human Subjects with waiver of informed consent/assent.

Data collection

The PICU and Pharmacy databases were used to identify subjects with fluid refractory catecholamine dependent septic shock. We screened for subjects with severe sepsis with or without shock based on ICD-9 codes (995.92 for severe sepsis and 785.52 for septic shock) from the PICU database (maintained by PICU-trained clinical data abstractors, who manually review patient records to ensure accurate data entry using ICD codes, specifically ICD-9 at the time of this study). Subsequently, we manually examined patient records to identify subjects with fluid refractory catecholamine dependent septic shock per the study definition detailed below. Data were collected on subject demographic characteristics, illness severity, duration of invasive mechanical ventilation support, duration and number of vasopressor infusions, dose and duration of SDH administered, duration of taper from SDH, and rSTC levels by querying the electronic medical record (EMR), and PICU and Pharmacy databases. Details regarding specialty consultation with Endocrinology to evaluate for adrenal insufficiency, and hypothalamic pituitary adrenal (HPA) axis testing were collected from the EMR. Data on primary and secondary outcomes were collected from the PICU database.

Definitions and outcomes

The cohort was dichotomized to subjects with rSTC level < 18 mcg/dL and subjects with rSTC level ≥ 18 mcg/dL. SDH therapy was defined as initial hydrocortisone dose 50 mg/m² (or 1 mg/kg, when length measurements were unavailable) followed by subsequent hydrocortisone dose 50 mg/m²/day (or 1 mg/kg/day, when length measurements were unavailable), administered via any route for one or more doses. Septic shock was defined as shock state due to suspected or proven sepsis requiring antimicrobial therapy. Fluid refractory catecholamine dependence was defined as the continuous need for catecholamine infusion for 6 or more hours following initial fluid resuscitation (≥ 60 ml/kg of crystalloid and/or colloid solutions) in septic shock. For the purpose of this study, catecholamines (vasopressors) were considered to include dopamine > 5 mcg/kg/minute, vasopressin (when used to support circulatory shock) as well as any dose of dobutamine, epinephrine, norepinephrine, phenylephrine, and milrinone. The vasopressor-inotrope score at the time of rSTC level measurement was calculated as: dopamine dose (mcg/kg/min) + dobutamine

dose (mcg/kg/min) + epinephrine (mcg/kg/min) $\times$ 100 + norepinephrine (mcg/kg/min) $\times$ 100 + phenylephrine (mcg/kg/min) $\times$ 100 + vasopressin (U/kg/min) $\times$ 10,000 + milrinone (mcg/kg/min) $\times$ 10 (19). Severity of illness was expressed as Pediatric Risk of Mortality (PRISM III) score at 12 hours (20).

The primary clinical outcome of interest was PICU mortality. Secondary clinical outcomes included PICU length of stay (LOS), hospital LOS, ventilator free days (VFD) at 28 days, vasopressor free days (VPFD) at 28 days, and hospital acquired infections (HAI). Liberation from invasive mechanical ventilation for > 24 hours and liberation from vasopressor infusion for > 24 hours defined duration of invasive mechanical ventilation and duration of vasopressor support, respectively. For the purpose of this study, non-invasive ventilation support did not count towards duration of invasive mechanical ventilation. VFD was determined by subtracting total ventilator days from 28 in survivors. VPFD was determined by subtracting total vasopressor days from 28 in survivors. All subjects with total ventilator days $\leq$ 28 days, and all PICU non-survivors were assigned VFD = 0. Similarly, all subjects with total vasopressor days $\leq$ 28 days and all PICU non-survivors were assigned VPFD = 0. HAI included central catheter associated bloodstream infections, catheter associated urinary tract infections, ventilator-associated infections, surgical site infections, and nosocomial viral infections based on National Healthcare Safety Network (NHSN) criteria utilized in our institution (21).

Statistical analysis

Summary data for subject characteristics and outcomes were expressed as mean values and standard deviations (SD) for normally distributed continuous variables, and as median values with inter-quartile ranges (IQR) for continuous variables that were not normally distributed. Categorical variables were reported as counts and percentages. We used t-test (or non-parametric equivalent, Wilcoxon rank sum) for analysis of differences between distributions of continuous variables, and Fisher's exact test for analysis of differences between distributions of categorical variables. We tested the association between SDH and PICU mortality, adjusted for severity of illness, using a two variable logistic regression model, and reported adjusted odds ratios (OR) with 95% confidence intervals (CI). Correlations between log-transformed rSTC levels and severity of illness (PRISM III scores) were tested with Pearson correlation. We did not correct our analyses for multiple comparisons and reported 2-sided p-values that were considered significant if $p < 0.05$.

Results

A total of 3583 patients were admitted to the PICU between January 1, 2013 and December 31, 2013, of whom 240 patients had a diagnosis of severe sepsis with or without shock. After excluding 170 patients (145 without catecholamine dependent septic shock i.e. fluid responsive, 18 with fluid refractory catecholamine dependent septic shock who received SDH but did not have measured rSTC levels, 3 with prior cardiac surgery within preceding six months and 4 with fluid refractory catecholamine dependent septic shock but had rSTC levels drawn after SDH administration), 70 subjects met inclusion criteria for study enrollment. The PICU mortality for the study cohort was 16% (11 deaths). Thirty (43%)

subjects had measured rSTC < 18 mcg/dL, while 42 (60%) subjects received SDH for fluid refractory catecholamine dependent septic shock. Of subjects who received SDH therapy, 90% (38/42) were dosed based on body surface area (BSA) calculated from length measurement obtained prior to SDH therapy. Specialty consultation with Endocrinology was obtained in 7 (10%) subjects to assess for adrenal insufficiency and HPA axis testing was performed in 3 (4%) subjects following completion of SDH therapy.

Outcomes by rSTC levels

In comparison to subjects with rSTC level < 18 mcg/dL (n = 30), subjects with rSTC level 18 mcg/dL (n = 40) were sicker with higher PRISM III scores at 12 hours and higher vasopressor-inotrope scores at the time of rSTC level measurement (Table 1, both $p < 0.05$). While 57% of subjects with rSTC level < 18 mcg/dL received SDH, up to 63% of subjects with rSTC level 18 mcg/dL received SDH ($p = 0.63$). The initial dose of SDH of 100 mg/m² was similar between the two groups (88% of subjects with rSTC level < 18 mcg/dL vs. 84% of subjects with rSTC level 18 mcg/dL, $p = 1$). There were no differences in the primary outcome of PICU mortality, or secondary outcomes of PICU LOS, hospital LOS, VFD, VPFD and HAI between the two groups based on rSTC cut-off level of 18 mcg/dL (Table 1).

Outcomes by SDH therapy

Subjects that received SDH therapy (n = 42) were sicker with higher PRISM III scores at 12 hours, higher vasopressor-inotrope scores at the time of rSTC level measurement, and required more support with mechanical ventilation at the time of SDH therapy in comparison to subjects that did not receive SDH therapy (n = 28) (Table 2). There were no significant differences in rSTC levels between the two groups ($p = 0.69$). Subjects with SDH therapy had higher PICU mortality than those without SDH therapy (unadjusted OR 8.4; 95% CI 1.2 – 70.2; $p = 0.049$). After adjusting for PRISM III scores at 12 hours, SDH therapy continued to be independently associated with PICU mortality (adjusted OR 6.7; 95% CI 2.6 – 42.1, $p = 0.039$). Subjects with SDH therapy also had worse secondary clinical outcomes in comparison to subjects without SDH therapy (Table 2). In the sub-group of subjects with rSTC level < 18 mcg/dL, there were no differences in PRISM III scores at 12 hours or vasopressor-inotrope scores at the time of rSTC level measurement between those that received SDH therapy and those that did not. In this sub-group, SDH therapy was associated with greater PICU LOS and hospital LOS, and fewer VFD (all $p < 0.05$) (Table 3). In the sub-group of subjects with rSTC level 18 mcg/dL, subjects that received SDH therapy were sicker with higher PRISM III scores at 12 hours and vasopressor-inotrope scores at the time of rSTC level measurement compared to those that did not receive SDH therapy. In this sub-group, SDH therapy was associated with higher PICU mortality, and fewer VFD and VPFD (all $p < 0.05$) (Table 3).

Relationships of rSTC levels, severity of illness and SDH therapy

Log-transformed rSTC levels were modestly positively correlated with PRISM III scores at 12 hours (Figure 1, $r = 0.3932$; $r^2 = 0.16$, $p < 0.001$). SDH therapy was not significantly different across quintiles of rSTC levels, with maximum exposure in the lowest and highest

quintiles (Figure 2a, $p = 0.177$). SDH therapy proportionately increased with PRISM III scores at 12 hours (Figure 2b, $p = 0.046$).

Discussion

The 2012 Surviving Sepsis Campaign pediatric guidelines recommend timely SDH therapy in children experiencing fluid refractory catecholamine dependent septic shock with suspected or proven absolute adrenal insufficiency, and also recommend obtaining an rSTC measurement prior to empiric SDH therapy (5). While the pediatric guidelines do not provide a clearly defined rSTC threshold level or make any recommendation on adrenocorticotrophic hormone (ACTH) stimulation testing, the adult guidelines explicitly recommend against using the ACTH stimulation test and state that “an inappropriately low random cortisol level (< 18 mcg/dL) in a patient with shock would be considered an indication for steroid therapy along traditional adrenal insufficiency guidelines” (Grade 2B – weak recommendation based on moderate quality evidence). Thus, the guidelines suggest that the rSTC level < 18 mcg/dL is a useful marker to identify the subset of patients who are sicker (presumably due to the added co-morbidity of adrenal insufficiency), and therefore more likely to benefit from SDH therapy resulting in improved clinical outcomes. The results of our study, however, do not support this recommendation. The sub-group of children with rSTC < 18 mcg/dL in our study were less sick with lower PRISM III scores at 12 hours and lower vasopressor-inotrope scores at the time of rSTC level measurement, in comparison to the sub-group with rSTC level ≥ 18 mcg/dL (Table 1). Further, SDH exposure in the sub-group with rSTC < 18 mcg/dL was associated with worse clinical outcomes in comparison to those not exposed to SDH within this sub-group (Table 3).

The findings of our study raise the important question of whether the rSTC level is the appropriate marker to identify adrenal insufficiency and to prospectively guide SDH therapy in critically ill children experiencing fluid refractory catecholamine dependent septic shock. While low rSTC levels in children with severe meningococemia may directly reflect acute adrenal insufficiency (Waterhouse-Friderichsen syndrome) (22–24), it is unclear whether rSTC levels directly correlate with adrenal function in the case of other critical illness settings such as non-meningococcal sepsis or trauma (25). The findings of our study are similar to other studies of critically ill children with severe sepsis (either alone, or in combination with other disease entities) that have observed strong positive correlation between rSTC levels and mortality, with higher levels in non-survivors (26–28). Elevated rSTC levels in these circumstances likely arise due to ACTH independent mediators of release as well as from decreases in metabolism and clearance of cortisol as an adaptive mechanism in times of acute stress (29,30). Simultaneously, ACTH concentrations decrease largely via negative feedback from elevated cortisol levels. This phenomenon of low ACTH and high cortisol has been termed “ACTH cortisol dissociation” and reflects HPA axis dysfunction in critical illness (30). Additionally, prolonged critical illness also appears to affect ACTH signaling with negative effects on adrenal structure and function that may result in decreased adrenal responsiveness to exogenous ACTH administration (31). These complex alterations in HPA axis function during critical illness clearly call into question our current choice of the rSTC level as a simplified biomarker of adrenal function during severe sepsis and/or septic shock.

Interestingly, we observed that SDH therapy correlated to a greater extent with severity of illness than rSTC levels, especially when rSTC level ≥ 18 mcg/dL. This raises the important question of whether clinicians felt compelled to attempt SDH therapy in critically ill children with greater severity of illness and more vasopressor support as a “last ditch” effort, particularly in those with rSTC level ≥ 18 mcg/dL who may have been at higher risk for worse outcomes. This “epiphenomenon” is similar to the well-described associations of worse outcomes with use of medications such as sodium bicarbonate and calcium during prolonged resuscitative efforts in pediatric cardiac arrest (32,33).

Our study adds to the growing debate about the appropriate indication for SDH therapy during fluid refractory catecholamine dependent pediatric septic shock based on current guidelines. As in other studies of critically ill children (13,14,28,34,35), SDH therapy conferred no definite benefits and, on the contrary, appeared to be associated with harm in this study cohort. Corticosteroids have numerous side effects including hyperglycemia, myopathy and delayed wound healing that predispose to morbidity and prolonged PICU dependency (36). Recent studies on gene expression have observed that adaptive immune response may be repressed by corticosteroids in children with septic shock (37). Additionally, higher risk subclasses in children with septic shock based on gene expression profiles appear to have worse outcomes with corticosteroid therapy (38).

The limitations of our study include the small sample from a single center. It is possible that clinician practice is different in other centers and the results from our single center may not be generalizable. Due to the retrospective design of the study, the potential for bias arises. In the absence of explicit clinician documentation of indication for SDH therapy, we assumed that SDH was used for management of fluid refractory catecholamine resistant shock in the relevant setting. It is also possible that a different threshold for rSTC level (e.g. 9 mcg/dL) might have resulted in different results, but the small number of subjects with rSTC level < 9 mcg/dL precluded us from being able to effectively test the discriminant ability of this level. Additionally, the observed association of SDH therapy with worse outcomes does not imply a direct causality.

While updated pediatric guidelines for therapy with SDH in children with septic shock are awaited, the recently published 2016 Surviving Sepsis Campaign adult guidelines recommend against SDH therapy if hemodynamic stability can be restored with adequate fluid resuscitation and vasopressor therapy (39). The updated adult guidelines also do not make any reference to a specific rSTC level threshold to initiate SDH therapy in patients with septic shock. Currently, the Steroids in Fluid and Vasoactive Infusion Dependent Pediatric Shock (STRIPES) is a pilot randomized controlled trial that is underway to assess feasibility of attempting a larger multi-center trial based on ability to recruit subjects, appropriateness of eligibility criteria and adherence to the treatment protocol (40). The larger trial is expected to help establish the role for SDH therapy in children with fluid and vasoactive infusion dependent shock.

Conclusions

SDH therapy in children with catecholamine dependent septic shock correlates more with severity of illness than rSTC levels and is associated with worse outcomes, irrespective of rSTC levels. Based on our pragmatic observations, the rSTC cut-off of 18 mcg/dL is a poorly discriminant marker for adrenal insufficiency in critically ill children with fluid refractory catecholamine dependent septic shock. A prospective randomized controlled trial is necessary to determine if stress dose hydrocortisone is efficacious and safe in fluid refractory catecholamine dependent septic shock in children.

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References

1. Weiss SL, Fitzgerald JC, Pappachan J, et al. Global epidemiology of pediatric severe sepsis: the Sepsis PRevalence, Outcomes, and Therapies study. *Am J Respir Crit Care Med*. 2015; 191:1147–57. [PubMed: 25734408]
2. Ruth A, McCracken CE, Fortenberry JD, et al. Pediatric severe sepsis: current trends and outcomes from the pediatric health information systems database. *Pediatr Crit Care Med*. 2014; 15:828–38. [PubMed: 25226500]
3. Balamuth F, Weiss SL, Neuman MI, et al. Pediatric severe sepsis in U.S. children's hospitals. *Pediatr Crit Care Med*. 2014; 15:798–805. [PubMed: 25162514]
4. Farris R, Weiss N, Zimmerman J. Functional outcomes in pediatric severe sepsis: further analysis of the researching severe sepsis and organ dysfunction in children: a global perspective trial. *Pediatr Crit Care Med*. 2013; 14:835–42. [PubMed: 24108117]
5. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med*. 2013; 41:580–637. [PubMed: 23353941]
6. Hebbbar KB, Stockwell JA, Leong T, et al. Incidence of adrenal insufficiency and impact of corticosteroid supplementation in critically ill children with systemic inflammatory syndrome and vasopressor-dependent shock. *Crit Care Med*. 2011; 39:1145–50. [PubMed: 21336126]
7. Hinshaw LB, Beller BK, Chang AC, et al. Corticosteroid/antibiotic treatment of adrenalectomized dogs challenged with lethal *E. coli*. *Circ Shock*. 1985; 16:265–77. [PubMed: 3902272]
8. Balis JU, Paterson JF, Shelley SA, et al. Glucocorticoid and antibiotic effects on hepatic microcirculation and associated host responses in lethal gram-negative bacteremia. *Lab Invest*. 1979; 40:55–65. [PubMed: 368436]
9. Schaefer CF, Brackett DJ, Wilson MF. The benefits of corticosteroid given after the onset of hypotension during endotoxin shock in the conscious rat. *Adv Shock Res*. 1983; 10:183–94. [PubMed: 6349297]
10. Annane D, Sébille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA*. 2002; 288:862–71. [PubMed: 12186604]
11. Sprung CL, Annane D, Keh D, et al. Hydrocortisone therapy for patients with septic shock. *N Engl J Med*. 2008; 358:111–24. [PubMed: 18184957]
12. Annane D, Bellissant E, Bollaert PE, et al. Corticosteroids for treating sepsis. *Cochrane Database Syst Rev*. 2015; 12:CD002243.
13. Markovitz BP, Goodman DM, Watson RS, et al. 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]

14. Zimmerman JJ, Williams MD. Adjunctive corticosteroid therapy in pediatric severe sepsis: observations from the RESOLVE study. *Pediatr Crit Care Med*. 2011; 12:2–8. [PubMed: 20228689]
15. Menon K, McNally D, Choong K, et al. A systematic review and meta-analysis on the effect of steroids in pediatric shock. *Pediatr Crit Care Med*. 2013; 14:474–80. [PubMed: 23867428]
16. Carmean A, Fortenberry JD, McCracken C, et al. A survey of attitudes and practices regarding the use of steroid supplementation in pediatric sepsis. *Pediatr Emerg Care*. 2015; 31:694–8. [PubMed: 26414641]
17. Menon K, McNally JD, Choong K, et al. A survey of stated physician practices and beliefs on the use of steroids in pediatric fluid and/or vasoactive infusion-dependent shock. *Pediatr Crit Care Med*. 2013; 14:462–6. [PubMed: 23628832]
18. Santschi M, Leclerc F. members of the Réseau Mère-Enfant de la Francophonie. Management of children with sepsis and septic shock: a survey among pediatric intensivists of the Réseau Mère-Enfant de la Francophonie. *Ann Intensive Care*. 2013; 3:7. [PubMed: 23497713]
19. Gaies MG, Gurney JG, Yen AH, et al. Vasoactive-inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass. *Pediatr Crit Care Med*. 2010; 11:234–8. [PubMed: 19794327]
20. Pollack MM, Patel KM, Ruttimann UE. PRISM III: an updated Pediatric Risk of Mortality score. *Crit Care Med*. 1996; 24:743–52. [PubMed: 8706448]
21. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control*. 2008; 36:309–32. [PubMed: 18538699]
22. Bone M, Diver M, Selby A, et al. Assessment of adrenal function in the initial phase of meningococcal disease. *Pediatrics*. 2002; 110:563–9. [PubMed: 12205261]
23. De Kleijn ED, Joosten KF, Van Rijn B, et al. Low serum cortisol in combination with high adrenocorticotrophic hormone concentrations are associated with poor outcome in children with severe meningococcal disease. *Pediatr Infect Dis J*. 2002; 21:330–6. [PubMed: 12075765]
24. Riordan FA, Thomson AP, Ratcliffe JM, et al. Admission cortisol and adrenocorticotrophic hormone levels in children with meningococcal disease: evidence of adrenal insufficiency? *Crit Care Med*. 1999; 27:2257–61. [PubMed: 10548217]
25. Vermes I, Beishuizen A, Hampsink RM, et al. Dissociation of plasma adrenocorticotropin and cortisol levels in critically ill patients: possible role of endothelin and atrial natriuretic hormone. *J Clin Endocrinol Metab*. 1995; 80:1238–42. [PubMed: 7714094]
26. Menon K, Ward RE, Lawson ML, et al. A prospective multicenter study of adrenal function in critically ill children. *Am J Respir Crit Care Med*. 2010; 182:246–51. [PubMed: 20299532]
27. Casartelli CH, Garcia PC, Branco RG, et al. Adrenal response in children with septic shock. *Intensive Care Med*. 2007; 33:1609–13. [PubMed: 17541546]
28. Yehya N, Vogiatzi MG, Thomas NJ, et al. Cortisol Correlates with Severity of Illness and Poorly Reflects Adrenal Function in Pediatric Acute Respiratory Distress Syndrome. *J Pediatr*. 2016; 177:212–218. e1. [PubMed: 27283464]
29. Boonen E, Vervenne H, Meersseman P, et al. Reduced cortisol metabolism during critical illness. *N Engl J Med*. 2013; 368:1477–88. [PubMed: 23506003]
30. Boonen E, Bornstein SR, Van den Berghe G. New insights into the controversy of adrenal function during critical illness. *Lancet Diabetes Endocrinol*. 2015; 3:805–15. [PubMed: 26071883]
31. Boonen E, Langouche L, Janssens T, et al. Impact of duration of critical illness on the adrenal glands of human intensive care patients. *J Clin Endocrinol Metab*. 2014; 99:4214–22. [PubMed: 25062464]
32. Raymond TT, Stromberg D, Stigall W, et al. Sodium bicarbonate use during in-hospital pediatric pulseless cardiac arrest - a report from the American Heart Association Get With The Guidelines[®]-Resuscitation. *Resuscitation*. 2015; 89:106–13. [PubMed: 25613362]
33. Srinivasan V, Morris MC, Helfaer MA, et al. Calcium use during in-hospital pediatric cardiopulmonary resuscitation: a report from the National Registry of Cardiopulmonary Resuscitation. *Pediatrics*. 2008; 121:e1144–51. [PubMed: 18450859]

34. Atkinson SJ, Cvijanovich NZ, Thomas NJ, et al. Corticosteroids and pediatric septic shock outcomes: a risk stratified analysis. *PLoS One*. 2014; 9:e112702. [PubMed: 25386653]
35. Menon K, McNally JD, Choong K, et al. A Cohort Study of Pediatric Shock: Frequency of Corticosteroid Use and Association with Clinical Outcomes. *Shock*. 2015; 44:402–9. [PubMed: 25692259]
36. Zimmerman JJ. A history of adjunctive glucocorticoid treatment for pediatric sepsis: moving beyond steroid pulp fiction toward evidence-based medicine. *Pediatr Crit Care Med*. 2007; 8:530–9. [PubMed: 17914311]
37. Wong HR, Cvijanovich NZ, Allen GL, et al. Corticosteroids are associated with repression of adaptive immunity gene programs in pediatric septic shock. *Am J Respir Crit Care Med*. 2014; 189:940–6. [PubMed: 24650276]
38. Wong HR, Cvijanovich NZ, Anas N, et al. Developing a clinically feasible personalized medicine approach to pediatric septic shock. *Am J Respir Crit Care Med*. 2015; 191:309–15. [PubMed: 25489881]
39. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Crit Care Med*. 2017; 45:486–552. [PubMed: 28098591]
40. O’Hearn K, McNally D, Choong K, et al. Steroids in fluid and/or vasoactive infusion dependent pediatric shock: study protocol for a randomized controlled trial. *Trials*. 2016; 17:238. [PubMed: 27153945]

Figure 1.

Scatterplot of correlation of pediatric risk of mortality (PRISM III) scores at 12 hours (x-axis) and log-transformed random serum total cortisol (rSTC) concentrations (y-axis).

Figure 2.

Figure 2(a). Stress dose hydrocortisone (SDH) therapy and random serum total cortisol (rSTC) levels.

Figure 2(b). Stress dose hydrocortisone (SDH) therapy and pediatric risk of mortality (PRISM III) scores at 12 hours.

Table 1

Characteristics of subjects with fluid refractory catecholamine dependent septic shock: by random serum total cortisol (rSTC) levels.

Characteristic	rSTC < 18 mcg/dL (n=30)	rSTC ≥ 18 mcg/dL (n=40)	p value
Age (months), median (IQR)	77 (27,174)	74 (19, 122)	0.42
Female, n (%)	15 (50)	28 (70)	0.14
Weight (kg), median (IQR)	20 (12, 41)	20 (11, 37)	0.47
Race			
White	16 (53)	17 (43)	0.60
Black	5 (17)	10 (25)	
Other	9 (30)	13 (32)	
Post-operative, n (%)	2 (7)	5 (13)	0.69
History of chronic steroid therapy, n (%)	4 (13)	4 (10)	0.72
Mechanical ventilation, n (%)	21 (70)	31 (78)	0.58
Number of vasopressors, median (IQR)	1 (1,2)	2 (2,2)	< 0.001
Vasopressor-inotrope score at time of rSTC level measurement, median (IQR)	10 (6,16)	18 (10,32)	0.007
PRISM III at 12 hours, median (IQR)	9 (5,15)	16 (8,22)	0.02
rSTC levels (mcg/dL), median (IQR)	12 (8,15)	30 (21,47)	< 0.001
SDH therapy, n (%)	17 (57)	25 (63)	0.63
Duration of SDH (days), median (IQR)	4 (2,4)	4 (2,5)	0.74
SDH taper, n (%)	12/17 (71)	16/25 (64)	0.75
Duration of SDH taper (days), median (IQR)	4 (3,5)	5 (4,11)	0.12
Outcomes			
PICU mortality, n (%)	3 (10)	8 (20)	0.33
PICU length of stay (days), median (IQR)	11 (3,19)	8 (4,22)	0.99
Hospital length of stay (days), median (IQR)	17 (9,28)	17 (8,39)	0.64
VFD at 28 days (days), median (IQR)	23 (17,28)	22 (8,25)	0.23
VPFD at 28 days (days), median (IQR)	26 (23,27)	25 (20,26)	0.17
Hospital acquired infection, n (%)	2 (7)	2 (5)	1

IQR: inter-quartile range; PRISM: pediatric risk of mortality; SDH: stress dose hydrocortisone; PICU: pediatric intensive care unit; VFD: ventilator free days; VPFD: vasopressor free days

Table 2

Characteristics of subjects with fluid refractory catecholamine dependent septic shock: treated with stress dose hydrocortisone (SDH).

Characteristic	SDH (n=42)	No SDH (n=28)	p value
Age (months), median (IQR)	82 (29,125)	52 (16,165)	0.58
Female, n (%)	27 (64)	16 (57)	0.62
Weight (kg), median (IQR)	21 (11, 31)	16 (11, 42)	0.88
Race			
White	21 (50)	12 (43)	0.80
Black	9 (21)	6 (21)	
Other	12 (29)	10 (36)	
Post-operative, n (%)	3 (7)	4 (14)	0.43
History of chronic steroid therapy, n (%)	7 (17)	1 (4)	0.13
Mechanical ventilation, n (%)	37 (88)	15 (54)	0.002
Number of vasopressors, median (IQR)	2 (1,2)	2 (1,2)	0.14
Vasopressor-inotrope score at time of rSTC level measurement, median (IQR)	16 (6,30)	11 (5,20)	0.02
PRISM III at 12 hours, median (IQR)	16 (10,25)	9 (6,15)	0.009
rSTC levels (mcg/dL), median (IQR)	21 (12,34)	19 (14,33)	0.69
Outcomes			
PICU mortality, n (%)	10 (24)	1 (4)	0.04
PICU length of stay (days), median (IQR)	10 (5,20)	4 (1,13)	< 0.001
Hospital length of stay (days), median (IQR)	19 (10,39)	10 (5,26)	0.003
VFD at 28 days (days), median (IQR)	21 (8,25)	28 (23,28)	< 0.001
VPFD at 28 days (days), median (IQR)	24 (20,26)	27 (25,27)	< 0.001
Hospital acquired infection, n (%)	3 (7)	1 (4)	0.65

IQR: inter-quartile range; PRISM: pediatric risk of mortality; rSTC: random serum total cortisol; PICU: pediatric intensive care unit; VFD: ventilator free days; VPFD: vasopressor free days

Table 3

Stress dose hydrocortisone (SDH) therapy in children with fluid refractory catecholamine dependent septic shock: by random serum total cortisol (rSTC) levels.

Characteristic	SDH	No SDH	p value
rSTC level < 18 mcg/dL	N = 17	N = 13	
Mechanical ventilation, n (%)	15 (88)	6 (46)	0.02
Number of vasopressors, median (IQR)	1 (1,2)	1 (1,2)	0.95
Vasopressor-inotrope score at time of rSTC level measurement	9 (6,18)	10 (5,17)	0.66
PRISM III at 12 hours, median (IQR)	10 (5,16)	11 (7,18)	0.48
rSTC levels, median (IQR)	11 (6,14)	14 (9,16)	0.23
Outcomes			
PICU mortality, n (%)	2 (12)	1 (8)	1
PICU length of stay, median (IQR)	11 (8,19)	2 (1,10)	0.002
Hospital length of stay, median (IQR)	19 (10,29)	6 (2,14)	0.003
VFD at 28 days, median (IQR)	22 (18,28)	28 (23,28)	0.03
VPFD at 28 days, median (IQR)	25 (23,27)	26 (22,27)	0.46
Hospital acquired infection, n (%)	1 (6)	1 (8)	1
rSTC level ≥ 18 mcg/dL	N = 25	N = 15	
Mechanical ventilation, n (%)	22 (88)	9 (60)	0.06
Number of vasopressors, median (IQR)	2 (2,3)	1 (1,2)	0.04
Vasopressor-inotrope score at time of rSTC level measurement	25 (14,36)	14 (6,22)	< 0.001
PRISM III at 12 hours, median (IQR)	20 (15,27)	8 (4,15)	< 0.001
rSTC levels, median (IQR)	31 (24,47)	22 (21,35)	0.04
Outcomes			
PICU mortality, n (%)	8 (32)	0 (0)	0.01
PICU length of stay, median (IQR)	8 (5,24)	7 (3,15)	0.22
Hospital length of stay, median (IQR)	25 (10,52)	14 (5,23)	0.18
VFD at 28 days, median (IQR)	20 (2,25)	25 (20,28)	0.04
VPFD at 28 days, median (IQR)	24 (12,25)	26 (24,27)	0.01
Hospital acquired infection, n (%)	2 (8)	0 (0)	0.52

IQR: inter-quartile range; PRISM: pediatric risk of mortality; PICU: pediatric intensive care unit; VFD: ventilator free days; VPFD: vasopressor free days