A Single-Center Review of Prescribing Trends and Outcomes of Corticosteroid Replacement Therapy in Critically Ill Children with Septic Shock

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Abstract: Recently published consensus treatment guidelines for pediatric sepsis recommend initiating corticosteroid replacement therapy (CRT) for those critically ill children with adrenal insufficiency and refractory shock. The data to support this recommendation is limited, and multiple studies have demonstrated significant variation in both the diagnosis and treatment of adrenal insufficiency and refractory shock in children. In order to better define the variation in practice at our institution, we retrospectively reviewed the experience with CRT in critically ill children with refractory septic shock over a 1-year-period. In addition, as a secondary aim we compared outcomes in critically ill children treated with CRT for variable lengths of time. We found that the initiation of CRT at our center is relatively consistent. However, we noted significant variation in the duration of CRT and whether CRT was gradually tapered or stopped abruptly. The majority of the patients in our cohort received less than the currently recommended duration of 7 days of CRT. There were a higher number of treatment failures in those patients who received CRT for greater than 7 days, suggesting that CRT should be tapered gradually in these patients. There is significant variation in prescribing trends for CRT at our institution, which are likely to be compounded in any multi-center cohort study of CRT in critically ill children with septic shock. Practice variation in CRT should be standardized to address the impact of CRT in this population.

Keywords: Sepsis, severe sepsis, adrenal insufficiency, pediatrics.

INTRODUCTION

Septic shock remains a significant health problem in critically ill children, accounting for close to $2 billion per year in healthcare expenditures in the United States alone [1]. Several noteworthy advances have contributed greatly to our understanding of the inherent complexities of the host inflammatory response at the cellular and molecular level in children with septic shock [2, 3]. However, in spite of these advances, septic shock continues to account for significant morbidity and mortality. Hospital mortality in critically ill children with septic shock approaches 10%, though mortality is slightly higher in children with pre-existing co-morbidities [1]. Comprehensive treatment guidelines for the management of septic shock have been recently published that specifically target the pediatric population [4]. These guidelines emphasize early resuscitation and reversal of shock, early administration of appropriate antibiotic therapy, and maintaining an adequate oxygen delivery using clinically relevant therapeutic endpoints. Importantly, the use of these guidelines has recently been associated with

improvement in outcomes [5, 6]. These management guidelines also emphasize initiating corticosteroid replacement therapy (CRT) in those children with adrenal insufficiency (AI), though there is relatively little data in the pediatric population to support this practice [7].

The potential efficacy of CRT in critically ill adults with septic shock [8] has fueled considerable debate regarding the appropriate definition and management of AI in critically ill children. Unfortunately, the lack of a universally accepted definition has made interpretation of study results complicated and identification of patients who might benefit from CRT difficult. The incidence of AI in critically ill children with septic shock ranges between 9 to 44%, depending upon which particular definition is used [9]. In addition, there is significant variation between available studies in the dose, duration of therapy, concomitant use of mineralocorticoid therapy (i.e. fludrocortisone), and whether a taper is used [10-12]. This lack of consensus precludes any meaningful comparison of studies or the routine practices between different pediatric intensive care units (PICUs). Regardless, there is at least some preliminary evidence that CRT may improve outcome in critically ill children with AI secondary to septic shock [7, 9, 13, 14]. We were therefore interested in examining our current practice to determine whether there is significant variation in the diagnosis and treatment of AI in critically ill children with septic shock at

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our institution, as the differences in prescribing trends at a single-institution would likely be magnified further in any multi-center trial enrolling critically ill children with septic shock. In addition, as a secondary aim, we sought to compare outcomes in critically children with septic shock who were treated with CRT with different dosages and for variable lengths of time.

MATERIALS AND METHODS

Setting

Cincinnati Children's Hospital Medical Center (CCHMC) is a 523-bed academic, quaternary-care, freestanding children's hospital. It is the only pediatric hospital in the Greater Cincinnati area and serves as a primary referral center for an eight-county area in southwestern Ohio, northern Kentucky, and southeastern Indiana. In fiscal year 2009, CCHMC had over 31,000 admissions and 114,000 emergency department visits and performed nearly 6,000 inpatient surgical procedures and 25,000 outpatient surgical procedures.

Study Participants

We conducted a retrospective review of all critically ill children admitted to the PICU at our institution with septic shock who were treated with CRT from December 31, 2006 to January 1, 2008. Approval was obtained from our hospital's investigational review board (IRB), and due to the retrospective nature of our study, the need for informed consent was waived. Patients were identified by searching the pharmacy database for all critically ill children with AI secondary to refractory shock who were treated with CRT. Patients were excluded if they had received corticosteroid therapy, for any reason, during the 14 days prior to admission to the PICU, had a history of Addison's disease, or were greater than 18 years of age. In addition, we excluded those children who received CRT following cardiopulmonary bypass for repair or palliation of congenital heart disease [15, 16]. Septic shock was diagnosed according to the consensus criteria developed by the Society of Critical Care Medicine (SCCM) and the American College of Chest Physicians (ACCP), modified specifically for pediatrics [17]. Refractory shock was defined as the need for vasoactive infusions following 60 mL/kg fluid resuscitation.

Our normal practice at Cincinnati Children's Hospital Medical Center is to evaluate all critically ill children with refractory septic shock for possible adrenal insufficiency *via* the cosyntropin stimulation test, using a computerized physician order entry (CPOE) order set. There are otherwise no formal guidelines or educational programs at our institution for standardizing coynstropin testing or CRT in critically ill children with septic shock. Briefly, a baseline cortisol level is obtained prior to the intravenous administration of cosyntropin at a dose of 0.25 mg. The dose of cosyntropin is reduced to 0.015mg/kg body weight for critically ill children less than one month of age. Serum cortisol is then measured at 30 and 60 minutes following administration of cosyntropin. Absolute adrenal insufficiency (AAI) is defined as a baseline cortisol level < 10 μg/dL (< 276 nmol/L), while relative adrenal insufficiency (RAI) is defined as incremental change at 60 minutes (Δ60) of < 9 μg/dL (< 248 nmol/L) [7]. In general,

CRT is administered to those critically ill children meeting criteria for either AAI or RAI. The dose of hydrocortisone, duration of therapy, and the length of the hydrocortisone taper (if used) is left to the discretion of the attending physician, based upon the results of the cosyntropin stimulation test and the patient's clinical condition or status. CRT is initiated, when indicated, as soon as the results of the cosyntropin stimulation test are made available.

Study Design and Data Collection

Patient demographic information including age, weight, height, Pediatric Risk of Mortality (PRISM)-III score [18], and diagnosis were collected *via* review of the electronic medical record (EMR), pharmacy database, and PICU database. The inotrope score [19] was calculated at one hour prior to initiation of CRT, 24 hours after initiation of CRT, and at subsequent 24 hour intervals during CRT until vasopressor therapy was discontinued or the patient expired. Briefly, the inotrope score is calculated as the sum of all inotrope doses, correcting for potency (dopamine, dobutamine=1 point for every 1 μg/kg/min; milrinone=10 points for every 1 μg/kg/min, and epinephrine=100 points for every 1 μg/kg/min) [19]. The duration of inotropic support was also determined. The results of the cosyntropin stimulation test, including the dose of cosyntropin administered and serum cortisol measured at baseline, 30 minutes, and 60 minutes after cosyntropin was recorded. The daily hydrocortisone dose per BSA, the total duration of CRT, the duration of CRT before beginning a taper (where applicable), and the duration of the corticosteroid taper was abstracted from the pharmacy database and EMR. Total length of stay in the PICU, survival to PICU discharge, and 28-day survival were determined.

Data Analysis

Abstracted data was tabulated in a Microsoft Excel 2003 spreadsheet (Microsoft, Redmond, WA) and analyzed using Sigmastat for Windows, version 3.11 (Systat Software, Inc, San Jose, CA). The indication for CRT was stratified into one of four groups, based upon a low baseline cortisol (≤10 μg/dL, 276 nmol/L), low incremental change following cosyntropin (Δ60 ≤9 μg/dL, 248 nmol/L), both, or neither (i.e. empiric therapy). We calculated the total duration of CRT (prospectively defined as the time from initiation to completion of CRT), the duration of CRT "stress dosing" (prospectively defined as the time from initiation of CRT to the initiation of a taper, when applicable), and the duration of the taper/wean (prospectively defined as the time when the dose of corticosteroid was gradually decreased until the time CRT was discontinued). Continuous variables were expressed as median (interquartile range) due to the non-parametric nature of the data. In order to determine whether the level of inotropic support impacted the decision to initiate CRT, we stratified patients into tertiles based upon the initial inotrope score and compared the total duration of CRT, duration of CRT "stress dosing," and duration of CRT taper (when applicable) between groups using one-way ANOVA. We also compared 28-day mortality between groups *via* Fisher's exact test.

Previous adult studies and a consensus guideline on the management of adrenal insufficiency in critically ill adults have recommended at least a minimum of 7 days of therapy,

once CRT is initiated [20]. We further stratified patients into two groups based upon the total duration of CRT (> 7 days CRT *vs* ≤ 7 days CRT). We prospectively defined "weaning failure" as a greater than 50% increase in the inotrope score after discontinuing CRT or if CRT was re-initiated for any reason after beginning a taper. We compared 28-day mortality between each group *via* Chi square test. We used Bonferroni's correction for multiple comparisons, and a p-value <0.05 was considered statistically significant.

RESULTS

During the 12-month period of review, 51 critically ill children were treated with CRT (Table **1**). Consistent with the previously described effects of etomidate on the hypothalamic-pituitary-adrenal (HPA) axis, approximately 20% of our patients had received treatment with etomidate at some point during the 48 hours before initiation of CRT [21]. Adrenal insufficiency was diagnosed based upon a cosyntropin stimulation test performed within 24 hours of admission to the PICU. All 51 children in our cohort had evidence of refractory septic shock based upon a median inotrope score at baseline of 13 (IQR 9, 39). CRT was initiated in 26/51 (51%) children due to a low baseline cortisol (AAI), while CRT was initiated in 19/51 (37%) due to a low Δ60 (RAI). CRT was initiated in 5/51 children (10%) due to both a low baseline cortisol and a low Δ60. CRT was initiated empirically in one child in the absence of either a low baseline cortisol or low Δ60. The majority of critically ill children (n=46/51, 90%) were treated with hydrocortisone at a total dose of 50 mg/m^2 BSA/day divided every 6 hours. Three children (6%) were treated with > 50mg/m^2 BSA/day and two children (4%) were treated with < 50mg/m^2 BSA/day for reasons that were not specified in the medical record. None of the children were treated with concomitant mineralocorticoid replacement therapy (e.g., fludrocortisones). A taper was used in 31/51 (60.7%) children with a median duration of 2 days (IQR 0, 7.5). CRT was discontinued abruptly in the remaining children. The median duration of CRT prior to initiating the taper in the cohort was 5 days (IQR 3, 8.5). The overall mortality in our cohort was 17.6 %, which is comparable to the reported mortality in previously published series of adrenal insufficiency secondary to pediatric septic shock [9, 14, 21-25].

Table 1.   Patient Demographics (n=51)

Age (mean), yrs	5.1 (0.1-17)
Weight, kg (mean ± SEM)	19.0 ± 2.2
Gender (M:F)	25:26
PRISM-III score, median (IQR)	12.8 (1-48)
Baseline Inotrope score, median (IQR)	30.7 (3-300)
Etomidate 48 hours prior to starting hydrocortisone, n (%)	10 (19.6%)

In order to determine whether the severity of illness at the initiation of CRT influenced prescribing trends, we stratified patients into tertiles based upon the initial inotrope score (Fig. **1**). There were no significant differences between the three groups with respect to the total duration of CRT, the duration of "stress dosing" of CRT (defined as the

duration on stress-dose hydrocortisone of at least 50 mg/m^2/day), and the duration of the taper (when applicable). There were no significant differences in 28-day mortality in the highest inotrope based upon initial inotrope score tertile (1st tertile: 11.8%; 2nd tertile: 11.8%; 3rd tertile: 27.8%; p=0.3).
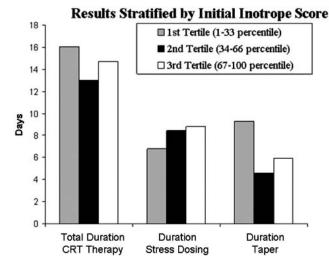

Fig. (1). CRT stratified by initial inotrope score.

Previous adult studies and a consensus guideline on the management of adrenal insufficiency in critically ill adults have recommended at least a minimum of 7 days of therapy, once CRT is initiated [20]. We therefore stratified patients by the duration of "stress dosing" CRT into two groups (> 7 days "stress dosing" CRT *vs* ≤ 7 days "stress dosing" CRT). Thirty-six (71%) patients were treated with "stress dosing" CRT for ≤ 7 days, while the remainder (15/51, 29%) received "stress dosing" CRT for > 7 days (median duration 13 days, IQR 9, 18). While there were no significant differences between these two groups, with respect to demographics, severity of illness, or baseline inotrope score, the number of weaning failures was significantly greater in patients that were treated for longer than 7 days CRT (Table **2**). The number of patients that failed the taper in each group was four and nine (11.1% and 60%) respectively (p < 0.001). Regardless, there was no difference in mortality between these two groups of patients.

DISCUSSION

We retrospectively reviewed the prescribing practices for CRT in critically ill children with septic shock at our institution over a 1-year period and noted significant variation with regards to duration of CRT and whether CRT was gradually tapered or stopped abruptly. Our data suggested that the initiation of CRT at our center is relatively consistent, with only one patient receiving CRT in the absence of a cosyntropin stimulation test. The majority of the patients in our cohort received less than the recommended seven days of CRT, though the period of study occurred prior to the release of the consensus guidelines [20]. There were a higher number of weaning failures in those patients who received CRT for greater than 7 days, suggesting that CRT should be tapered gradually in these patients.

We did not specifically analyze the factors that were associated with variation in prescribing practices for CRT.

Table 2. **Patient Demographics and Outcome Based Upon Duration of CRT**

	≤ 7 Days Stress Dose CRT	**> 7 Days Stress CRT**
N (%)	36 (70.6%)	15 (29.4%)
Duration of Inotropes (h), median (IQR)	76 (41, 83)	59 (56.75, 217.75)
Duration of Hydrocortisone Taper (days), median (IQR)	2 (0, 6)	5 (0.75, 13.5)
Weaning failure, n (%)	4/36 (11.1%)[†]	9/15 (60%)[†]
Mortality (%)	6/36 (16.7%)[‡]	3/15 (20%)[‡]

[†]: $p<0.001$, [‡] $p=$NS.

All of the treatment decisions regarding CRT were made by the attending PICU physician. All of the attending PICU physicians at our institution have completed approved pediatric critical care medicine fellowship training programs and are either board-eligible or board-certified in pediatric critical care medicine. The experience ranges between 2 to 15 years of practice following completion of training. It is possible that varying levels of experience or differences in fellowship training contributed to the variation in practice. Alternatively, patient factors may have biased treatment decisions. However, neither the severity of illness (based upon initial inotrope score) nor the time on vasoactive infusions affected the duration of CRT or use of a taper. Regardless, we feel that a multi-center study will be necessary to further define the variation in prescribing patterns for CRT in critically ill children.

Corticosteroids have been used in the management of critically ill patients with septic shock for the last several decades [26]. The approach until the early 1980's focused on administering very high, supraphysiologic doses of corticosteroids in an attempt to block the host inflammatory response – consistent with the prevailing theory of the pathophysiology of sepsis at the time. Unfortunately, large, multi-center, randomized, placebo-controlled trials failed to show any benefits to this practice [27, 28]. Two subsequent meta-analyses [29, 30] failed to demonstrate any benefit to high-dose corticosteroid administration in this patient population, and the practice was largely abandoned [7]. More recently, there has been a resurgence of interest in the use of corticosteroids in the management of critically ill patients with septic shock. Following the promising results of smaller studies that suggested a benefit to moderate-dose corticosteroids [31, 32], Annane and co-workers [33] conducted a multi-center, randomized, placebo-controlled, double-blind trial comparing the use of stress-dose hydrocortisone (50 mg i.v. every 6 hours) and fludrocortisone (50 μg once daily) or placebo in critically ill adults with septic shock and adrenal insufficiency (as determined by an inadequate response to cosyntropin stimulation test). While the trial suffered from some methodologic concerns [26], there was a significant reduction in the duration of vasopressor therapy and 28-day mortality in patients with adrenal insufficiency who were randomized to the treatment group.

The results of the Corticosteroid Therapy of Septic Shock (CORTICUS) trial [34] were recently published, in which hydrocortisone treatment shortened the duration of time to shock reversal in patients with an inadequate cortisol response to cosyntropin, as well as those patients who did respond with an adequate cortisol response to cosyntropin. However, there was no difference in 28-day mortality in either the responder group or non-responder group in patients randomized to hydrocortisone treatment *vs* placebo. The trial was underpowered to detect a difference in mortality, as the trial was prematurely terminated after only 500 of the planned 800 subjects were enrolled due to slow enrollment.

Unfortunately, there have been no prospective, randomized, placebo-controlled trials of CRT in critically ill children with septic shock. Despite the lack of available data, CRT is commonly prescribed in the vast majority of PICUs throughout North America [10, 11] and the United Kingdom [13]. For example, in one recent survey, 51% of Canadian pediatric intensivists stated that they would treat refractory septic shock with CRT [10]. In an electronic survey of pediatric intensivists who subscribe to the PICUList e-mail discussion group, 48% of those responding stated that they routinely prescribe CRT based upon the presence of refractory septic shock and in the absence of cosyntropin testing. Moreover, 68% of those surveyed stated that they would not participate in any study that would potentially randomize critically ill children with refractory septic shock to a placebo-arm [11]. All three surveys noted wide variation in both prescribing practices and diagnosis of adrenal insufficiency [10, 11, 13], consistent with the results of the current study.

The current consensus guideline on the management of adrenal insufficiency in critically ill adults recommends at least a minimum of 7 days of therapy, once CRT is initiated [20]. Given the relative paucity of data in critically ill children, we stratified patients based upon the duration of CRT (> 7 days CRT *vs* ≤ 7 days CRT). While there was no difference in mortality between these two groups of patients, the number of weaning failures was significantly greater in patients that were treated for longer than 7 days CRT, suggesting that a taper is warranted in this population rather than abruptly terminating therapy. The optimal duration of therapy in both critically ill children and adults with AI is not known. However, the consensus guidelines currently recommend tapering CRT rather than stopping treatment abruptly.

Our findings are certainly limited by the retrospective nature of our study and may not be applicable outside our own institution. However, the significant variation in CRT

prescribing practices at our single-institution are likely to be compounded even further in any multi-center, cohort study, making it difficult, if not impossible, to compare and analyze outcomes in critically ill children receiving CRT for refractory septic shock. The significant variation in CRT practice noted by the aforementioned surveys [10, 11, 13] would appear to support this conclusion.

Given the paucity of clear-cut evidence for CRT in both critically ill children [7] and adults [34], we feel that a prospective, randomized, placebo-controlled trial of CRT in the PICU is clearly warranted [11, 35]. However, there are several potential barriers to the completion of such a trial [7]. First and foremost, as the results of the current study suggest, there is significant variation in practice regarding both the diagnosis and treatment of AI in critically ill children with septic shock. Moreover, there is significant variation in practice with regards to the diagnosis and management of critically ill children with septic shock. Second, critically ill children with septic shock have a relatively low mortality rate compared to adults, such that thousands of patients in both the therapy and control groups would be necessary for a sufficiently powered study using the traditional 28-day mortality as primary outcome. Finally, there is perhaps lack of equipoise for conducting a trial in which critically ill children are randomized to placebo or CRT. With these substantial barriers in mind, we believe that a multi-center cohort study using historical controls and in which practice variation is minimized could provide important, supportive evidence for CRT in this population. We suggest that CRT prescribing practices should be standardized in order to minimize variation and allow for meaningful comparison between centers.

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