The Association of Early Corticosteroid Therapy With Clinical and Health-Related Quality of Life Outcomes in Children With Septic Shock*

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OBJECTIVES: Corticosteroids are commonly used in the treatment of pediatric septic shock without clear evidence of the potential benefits or risks. This study examined the association of early corticosteroid therapy with patient-centered clinically meaningful outcomes.

DESIGN: Subsequent cohort analysis of data derived from the prospective Life After Pediatric Sepsis Evaluation (LAPSE) investigation. Outcomes among patients receiving hydrocortisone or methylprednisolone on study day 0 or 1 were compared with those who did not use a propensity score–weighted analysis that controlled for age, sex, study site, and measures of first-day illness severity.

SETTING: Twelve academic PICUs in the United States.

PATIENTS: Children with community-acquired septic shock 1 month to 18 years old enrolled in LAPSE, 2013–2017. Exclusion criteria included a history of chronic corticosteroid administration.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Among children enrolled in LAPSE, 352 of 392 met analysis inclusion criteria, and 155 of 352 (44%) received early corticosteroid therapy. After weighting corticosteroid therapy administration propensity across potentially confounding baseline characteristics, differences in outcomes associated with treatment were not statistically significant (adjusted effect or odds ratio [95% CI]): vasoactive-inotropic support duration (−0.37 d [−1.47 to 0.72]; $p = 0.503$), short-term survival without new morbidity (1.37 [0.83–2.28]; $p = 0.218$), new morbidity among month-1 survivors (0.70 [0.39–1.23]; $p = 0.218$), and persistent severe deterioration of health-related quality of life or mortality at month 1 (0.70 [0.40–1.23]; $p = 0.212$).

CONCLUSIONS: This study examined the association of early corticosteroid therapy with mortality and morbidity among children encountering septic shock. After adjusting for variables with the potential to confound the relationship between early corticosteroid administration and clinically meaningful end points, there was no improvement in outcomes associated with this therapy. Results from this propensity analysis provide additional justification for equipoise regarding corticosteroid therapy for pediatric septic shock and ascertain the need for a well-designed clinical trial to examine benefit/risk for this intervention.

KEY WORDS: corticosteroids; health-related quality of life; mortality; outcomes; septic shock; vasoactive-inotropic support

Sepsis is one of the leading causes of pediatric morbidity and mortality worldwide (1). Improving the outcomes and establishing an evidence-based standard of care for these patients remain an ongoing quest. Although rigorous investigative and quality improvement efforts have reduced overall mortality in pediatric sepsis, significant, enduring morbidity burdens

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children surviving sepsis, with 24–35% of patients suffering significant, persistent deterioration of health-related quality of life (HRQL) and/or functional status (FS) (2–6). There is ongoing investigation in this area, with the goal of describing factors that contribute to FS and HRQL following sepsis in children.

It has been repeatedly documented that severity of sepsis illness is strongly associated with morbidity. Critical illness factors such as extent and duration of organ failure and shock are independently associated with persistent, serious deterioration of HRQL in children surviving a septic shock event (7). Patient factors, such as older age and immune compromise, have also been implicated (6). However, little is definitively known regarding the effect treatment factors, such as adjunctive pharmacologic therapies, have on mortality/morbidity outcomes related to pediatric septic shock.

Corticosteroids are one of the most commonly used adjunctive therapies for children with septic shock (8–12). The true effect of this therapy on sepsis mortality and morbidity is unknown as large, well-designed pediatric interventional trials are lacking, albeit in progress (NCT03401398). Corticosteroid side effects, such as immune suppression, myopathy, hyperglycemia, and salt/water retention, have the potential to worsen the outcomes of children with septic shock (13). In fact, elegant gene expression analyses of children with sepsis have identified endotypes associated with increased or decreased risk of mortality with corticosteroid prescription (14, 15).

Although several previous investigations (mostly retrospective descriptive cohort studies) (2, 8–11, 14, 16, 17) have examined the potential benefits and risks of corticosteroid therapy for pediatric septic shock, we sought to examine this same question in a planned secondary analysis of the Life After Pediatric Sepsis Evaluation (LAPSE) database utilizing the propensity balancing methodology with a focus on mortality/morbidity outcomes assessed at 1 month following PICU admission.

MATERIALS AND METHODS

LAPSE (R01HD073362) was a prospective, observational cohort investigation conducted at 12 major pediatric critical care centers across the United States from 2013 to 2017 (5, 7). Children 1 month to 18 years old with community-acquired septic shock were enrolled. Septic shock was defined as: documented or suspected infection with onset within 48 hours of hospital admission and presence of at least two systemic inflammatory response syndrome criteria, including abnormal leukocyte count and/or abnormal body temperature (18), and need for fluid resuscitation, and vasoactive/inotropic support initiated within 72 hours of admission to the hospital and 48 hours of PICU admission. Other details of the LAPSE protocol may be found in (5). Patients identified by research personnel as immunocompromised due to corticosteroid use prior to hospitalization were considered at high risk for absolute adrenal insufficiency and excluded from this secondary analysis.

Initial demographic information, initial illness severity, and baseline FS and HRQL scores (reflecting patient status in the month prior to the sepsis event) were collected around the time of PICU admission. Pediatric RISk of Mortality (PRISM) III was evaluated at the time of PICU admission using the worst physiologic values from –2 to 4 hours after PICU admission (19). Vasoactive-Inotropic Score (VIS) was calculated bid (0,800 and 2,000), and Pediatric Logistic Organ Dysfunction (PELOD-2) scores were collected daily until PICU discharge, death, or day 28, whichever came first (20).

Under institutional review board oversight (**eText 1**, http://links.lww.com/PCC/C115), documented, informed parental permission was obtained before any LAPSE study procedures were undertaken. Developmentally appropriate patients were requested to provide assent for their own continued study participation following PICU discharge. Management of patients, including the use of corticosteroids, was left to attending physician discretion.

The primary aim of this LAPSE ancillary investigation was to evaluate the association of early corticosteroid therapy with resolution of shock (vasoactive-inotropic support-free days), month-1 survival, month-1 survival without new morbidity, and survival to month 1 with no severe reduction in HRQL compared with prehospital baseline. Vasoactive-inotropic support-free days were defined as 28 minus the number of days (up to 28) of vasoactive-inotropic support use for 28-day survivors. Patients who died before day 28 were assigned zero vasoactive-inotropic support-free days. New morbidity was defined as

a worsening in Functional Status Score by 3 or more points from baseline to hospital discharge or day 28, whichever came first (21). HRQL was measured using the Stein Jessop Functional Status version II-R (FSII-R) for severely developmentally delayed subjects and the Pediatric Quality of Life Inventory for others according to parent preference (5, 22–24). Data quantifying HRQL were collected on enrollment and at the month-1 follow-up (days 21–42). Persistent, severe deterioration (PSD) in HRQL was defined as more than a 25% decrease compared with prehospital baseline. Secondary outcomes were mechanical ventilation-free days, PICU-free days, hospital-free days, and sum of PELOD-2 scores during PICU stay, truncated at 28 days. These outcomes were selected a priori as the primary and secondary outcomes that might be affected by the use of corticosteroids.

Early corticosteroid therapy was defined as initiation of hydrocortisone or methylprednisolone on study day 0 or 1. Study day 0 was defined as the time of PICU admission to 2,359 that day. All other days described a 24-hour time period from 0,000 to 2,359. If steroids were prescribed, the name of the corticosteroid and the total 24 hour dose were recorded for each study day. Time of initiation was not recorded, limiting a more narrow time period for the inclusion criteria. Patients who received early corticosteroid therapy were included in the "Early Corticosteroid" group. Patients who did not receive early corticosteroid therapy were included in the "No Early Corticosteroid" group, regardless of steroid use after days 0 and 1 or systemic steroid use other than hydrocortisone or methylprednisolone on days 0 and 1 (such as dexamethasone). Patients receiving methylprednisolone were included in the Early Corticosteroid group because at the dose most commonly prescribed (1–2 mg/kg/d), potentially beneficial hemodynamic and anti-inflammatory actions might be expected, although the mineralocorticoid and glucocorticoid effects of methylprednisolone are considered to be five times as potent as hydrocortisone (25). In order to more fully understand how this approach might impact results, a sensitivity analysis was conducted in which the patients receiving methylprednisolone only (no hydrocortisone) during the treatment window were included in the "No Early Corticosteroid" group, and primary outcomes were analyzed. In the PICU, dexamethasone is most commonly used for its anti-inflammatory properties to decrease airway swelling in preparation for extubation. Dexamethasone is not considered adjunctive therapy for sepsis. Thus, patients who received dexamethasone on day 0 or 1 were included in the "No Early Corticosteroid" group.

Baseline factors have the potential to confound the relationship between early corticosteroid therapy and outcomes. Accordingly, a propensity score method was used to minimize the effects of confounding by constructing a weighted cohort of subjects balanced with respect to baseline characteristics, but differing with respect to corticosteroid therapy (26). Baseline characteristics identified a priori as likely confounders included age, sex, study site, PRISM III, and highest First-Day VIS. Effect estimates for these characteristics were not reported or investigated as they were solely used in a logistic regression model to predict the probability (propensity) of corticosteroid therapy for each subject in the cohort. A balanced cohort was constructed in which subjects were weighted using stabilized inverse treatment probability weighting. This approach more heavily weights subjects receiving therapy different from what was predicted by the logistic regression model considering baseline characteristics. Minimum, maximum, mean, and SD of the weights were assessed. Absolute standardized differences between treatment and control groups were reported for baseline characteristics in the original cohort. Absolute standardized differences measure the difference of means for continuous variables and the difference of proportions for categorical variables between those receiving corticosteroid therapy versus those who did not. Differences in each baseline characteristic were standardized in terms of the standard deviations in both the treated and the nontreated groups. Absolute standardized differences of less than or equal to 0.10 were considered to indicate a well-balanced cohort in which the effects of confounding have been removed. If the absolute standardized difference exceeded 0.10, the covariate was additionally controlled for in the outcome model.

After achieving satisfactory balance and finalizing the propensity model, logistic regression models for the different outcomes were created using the weighted cohort, with early corticosteroid therapy included as the primary predictor. These weighted regression models also controlled for PRISM III, as it is known to be a strong predictor of outcomes in question (8). By addressing confounding in both ways (weighted

cohort and covariates), bias is less dependent on model specification. Additionally, by controlling for variables explicitly that are considered strong predictors of outcomes, we potentially reduce the variability of our estimated effect, improving power and narrowing CIs (27). The estimated effect of therapy on outcomes was summarized using odds ratios for binary outcomes and effect sizes for continuous variables such as vasoactive-inotropic support-free days.

Substantial loss to follow-up was observed at month 1 in the original LAPSE cohort. To investigate the potential bias missing month-1 HRQL measures may have introduced, sensitivity analyses were performed using multiply-imputed data. The multiple imputation techniques used in this investigation closely mirrored those of previously published LAPSE articles (5, 7), with the exception that a more robust number of imputed datasets were generated ($n = 50$).

Reported p values were based on a two-sided alternative hypothesis and considered significant if less than 0.05. No adjustment was made for multiple comparisons. Analyses were performed using SAS Version 9.4 (SAS Institute, Cary, NC).

RESULTS

Out of 392 patients enrolled in the LAPSE study, 352 patients met analysis eligibility criteria (**Fig. 1**). Thirty-four patients were excluded due to prehospitalization chronic corticosteroid administration. Six patients withdrew or had insufficient baseline clinical data. Month-1 follow-up HRQL data were available for 205 patients. Twenty-four patients died during or before the month-1 follow-up period.

Patient Characteristics

Baseline characteristics of the 352 patients included in the propensity analysis can be found in **Table 1**. These characteristics (sex, clinical institution, age, PRISM III, and highest First-Day VIS) were determined a priori to be potentially confounding factors associated with both early adjunctive corticosteroid therapy and outcome. Propensity score distribution among patients in each group can be found in **eFigure 1** (http://links.lww.com/PCC/C115). After propensity weighting, the absolute standardized difference between the treatment and no treatment group was less than or equal to 0.10 for all identified potentially confounding variables other than clinical site I, which achieved 0.11 absolute standardized difference. Thus, site I was included as a covariate in the outcome model along with PRISM III.

Corticosteroid Use

Overall, 65% of patients (229/352) received any systemic corticosteroid during their PICU stay. Among those who received adjunctive corticosteroids, hydrocortisone was most commonly reported (143/229, 62%), followed by dexamethasone (77/229, 33.6%), and methylprednisolone (65/229, 28%). Of the patients who received hydrocortisone or methylprednisolone, therapy was initiated on days 0 and 1 in 155 of 208 of the cases (7,575%). Thus, 155 patients (44%) were placed in the Early Corticosteroid Group. Twelve of these patients received both hydrocortisone and methylprednisolone on days 0 and 1. As defined by study criteria, 197 patients did not receive early corticosteroid therapy. Patients treated with hydrocortisone received a median dose of 1.9 mg/kg/d for a median of 5 calendar days on study. The median dose of methylprednisolone was also 1.9 mg/kg/d administered for a median duration of 6 calendar days. Additional information, including systemic steroid administration during the treatment window, average mg/kg/day dosing, and duration of therapy for each systemic corticosteroid, can be found in **Table 2**.

Effect of Adjunctive Corticosteroid Use on Outcomes

The estimated effect of adjunctive corticosteroid use on all outcomes is summarized in **Tables 3** and **4**. There was no significant difference in vasoactive-inotropic support-free days, duration of vasoactive-inotropic support, survival to month 1, or survival to month 1 without new morbidity associated with early adjunctive corticosteroid therapy. In those with complete month-1 follow-up data ($n = 205$), there was no significant difference in HRQL outcomes between the two groups. Additionally, there was no significant difference in hospital-free days, PICU-free days, sum of PELOD-2 during PICU admission, or ventilator-free days between the groups. Outcome data prior to propensity analysis are available for reference in **eTable 4** (http://links.lww.com/PCC/C115). Results from the sensitivity analysis, in which patients receiving only methylprednisolone were placed in the "No Early

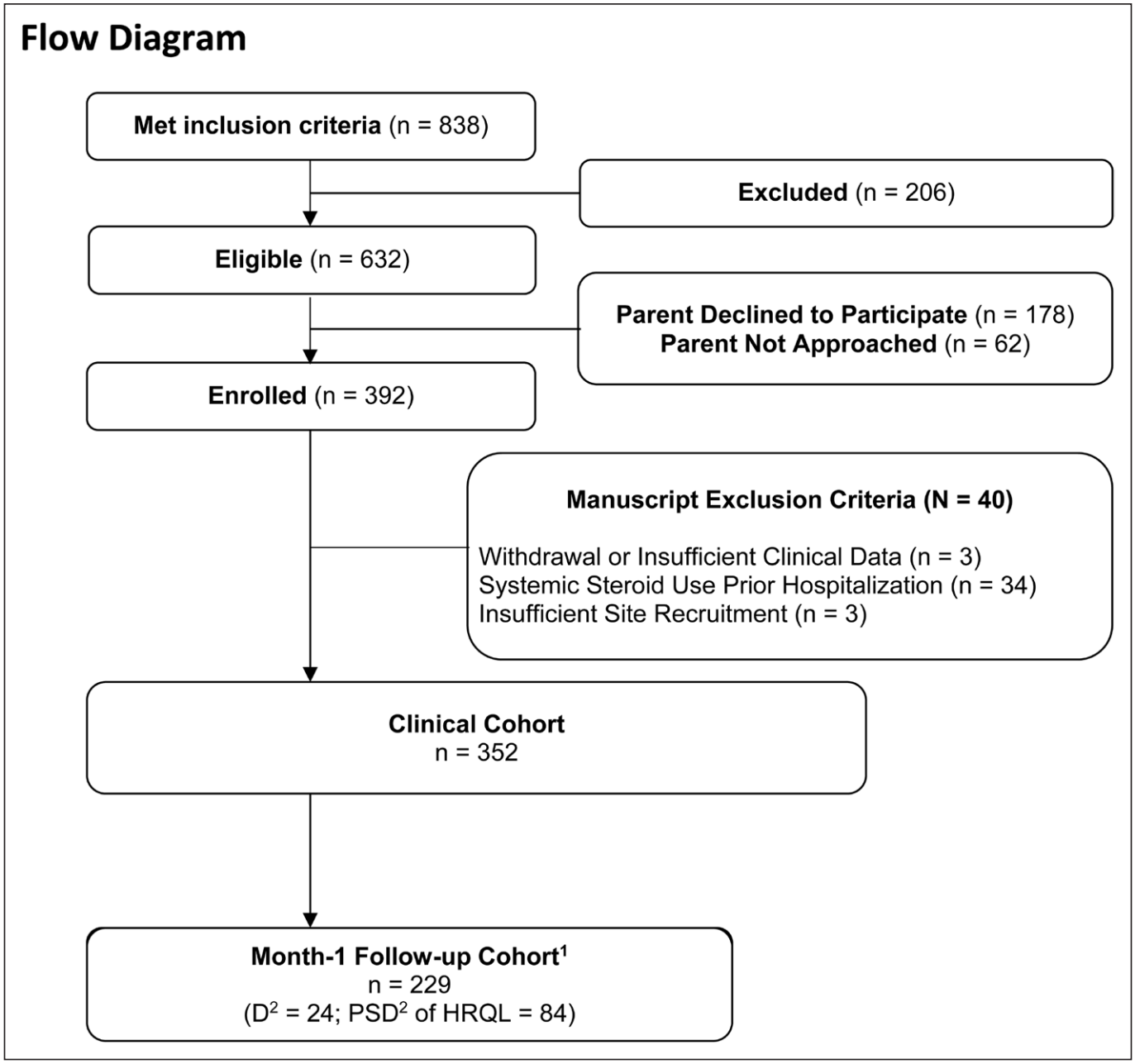

Figure 1. [1]Cohort includes patients with a month-1 health-related quality of life (HRQL) assessment (collected day 21–day 42) or patients who died during or before the month-1 follow-up period. [2]D represents cumulative deaths among the entire LAPSE clinical cohort at month 1. PSD = persistent, severe deterioration of HRQL below baseline, specifically, HRQL scores (Pediatric Quality of Life Inventory [PedsQL] or Functional Status version II-R [FSII-R]) persisting greater than 25% below the baseline HRQL.

Corticosteroid" group, were similar (**eTables 5** and **6**, http://links.lww.com/PCC/C115), again with no significant estimated effect of early hydrocortisone therapy demonstrated for any of the primary outcomes.

Because loss to follow-up at month-1 was substantial, we used the imputation methods described above to analyze an additional 80 patients for the composite outcome of mortality or PSD (n = 328) and an additional 72 patients for PSD (n = 308) at month 1. Odds ratio estimates and 95% CIs for early corticosteroid therapy using imputed data (**eTables 1** and **2**, http://links.lww.com/PCC/C115) compared with the complete case analysis (**Table 3**) showed no evidence of substantial bias due to missing HRQL data at month 1. Cohort characteristics of those with complete HRQL data were compared with those who were lost to follow-up (**eTable 3**, http://links.lww.com/PCC/C115). The patients who were lost to follow-up differed only by study site, whereas markers of illness severity were not statistically different.

TABLE 1.
Baseline Characteristics Determined to be Potentially Confounding Factors Associated With Both Early Corticosteroid Therapy and Outcome

	Cohort Before ITP Weighting			Cohort After ITP Weighting[a]		
Baseline Characteristic	Early Corticosteroid (*n* = 155)	No Early Corticosteroid (*n* = 197)	Absolute Standardized Difference	Early Corticosteroid	No Early Corticosteroid	Absolute Standardized Difference
Female	76 (49%)	87 (44%)	0.10	68 (44%)	88 (45%)	0.02
Clinical institution						
Site A	41 (26%)	39 (20%)	0.16	37 (24%)	51 (26%)	0.05
Site B	4 (3%)	10 (5%)	0.13	5 (3%)	7 (4%)	0.02
Site C	7 (5%)	11 (6%)	0.05	8 (5%)	10 (5%)	< 0.01
Site D	19 (12%)	6 (3%)	0.35	11 (7%)	14 (7%)	< 0.01
Site E	9 (6%)	31 (16%)	0.32	19 (12%)	23 (12%)	0.02
Site F	14 (9%)	8 (4%)	0.20	9 (6%)	10 (5%)	0.04
Site G	18 (12%)	19 (10%)	0.06	15 (10%)	18 (9%)	0.01
Site H	11 (7%)	16 (8%)	0.04	10 (6%)	13 (7%)	0.02
Site I	9 (6%)	23 (12%)	0.21	19 (12%)	18 (9%)	0.11
Site J	5 (3%)	15 (8%)	0.19	7 (5%)	11 (6%)	0.05
Site K	12 (8%)	8 (4%)	0.16	9 (6%)	11 (6%)	< 0.01
Site L	6 (4%)	11 (6%)	0.08	7 (5%)	10 (5%)	0.02
Age						
0–24 mo	37 (24%)	65 (33%)	0.20	49 (32%)	61 (31%)	0.02
2–17 yr	118 (76%)	132 (67%)	0.20	106 (68%)	136 (69%)	0.02
Pediatric Risk of Mortality III	13.6 ± 8.62	10.2 ± 7.14	0.43	11.3 ± 8.20	11.0 ± 7.20	0.04
Highest Vasoactive-Inotropic Score, first day[b]	17.5 ± 19.12	8.5 ± 8.52	0.60	11.9 ± 14.96	11.0 ± 11.46	0.06

ITP = inverse treatment probability.

[a]Counts may not sum to expected totals and percentages may not total 100 due to rounding.

[b]First day was defined as day of admission if admission time was before 12:00 PM or following day if admission was after 12:00 PM.

Continuous variables are represented as mean ± SD, while dichotomous variables are represented as *n* (%).

DISCUSSION

This study examined the association of early corticosteroid therapy with clinically meaningful outcomes such as FS and HRQL among children encountering septic shock using a propensity-weighted analysis. The results of this study did not reveal any significant associated improvement or worsening of survival, HRQL, or FS among patients who received early corticosteroid therapy. Additionally, there was no associated improvement in the duration of vasoactive-inotropic support, ventilator-free days, duration of organ dysfunction, or resource utilization.

The most common reason pediatric critical care practitioners prescribe adjunctive corticosteroids in septic shock is to achieve hemodynamic stability in the setting of escalating vasoactive-inotropic support. Corticosteroids may improve the hemodynamics of an individual in shock in multiple ways including improving myocardial contractility and vasomotor tone by increasing calcium availability (28), increasing β-adrenergic receptor sensitivity and expression (29), decreasing the reuptake of norepinephrine (28), and decreasing production of nitric oxide and prostacyclin (30). This drug class stimulates intracellular adhesion factors that may play a role in capillary leak

TABLE 2.
Corticosteroid Characterization

Corticosteroid Administered	Frequency of Use Days 0–1 *n/N* (%)	Frequency of Use on Study *n/N* (%)	Amount[a] (mg/kg/d)	Duration[b] (d)
Any steroid	160/352 (45)	229/352 (65)	–	–
Hydrocortisone	120/160 (75)	143/229 (63)	1.9 (0.9–3.0)	5 (3–8)
Methylprednisolone	47/160 (29)	65/229 (28)	1.9 (1.0–2.9)	6 (3–8)
Dexamethasone	5/160 (3)	77/229 (34)	0.5 (0.3–1.0)	2 (1–3)
Prednisone or prednisolone	0/160 (0)	18/229 (8)	1.1 (0.9–2.0)	2 (1–6)

[a]There were 25 of 1,664 daily corticosteroid administration totals where the value entered was unable to be converted to mg/kg/d.
[b]Corticosteroid administrations were recorded on study days 0–28 inclusive. Duration is defined as the sum of calendar days the patient was administered steroids. Each steroid duration summary only includes patients receiving the medication.
Median (Q1–Q2) are reported for continuous summaries.

(31). Clinically, early hydrocortisone supplementation has been shown to increase blood pressure and hasten the resolution of shock in adults and children (32–38). El-Nawawy et al (39) corroborated these findings in children with septic shock but failed to prove that corticosteroids improved patient-centered outcomes such as mortality. Our study failed to document a decrease in vasoactive-inotropic support. This may be due to the limited (twice daily) reporting of the VIS with more subtle VIS differences potentially missed. Similarly, reporting the duration of vasoactive-inotropic support in units of nearest days increases the likelihood of missing a significant difference, despite previous studies being able to do so (39). It is plausible that more granular vasoactive-inotropic support data may have allowed us to demonstrate a difference with early corticosteroid therapy, but the LAPSE investigation was not designed to do so. It is also plausible that there truly is no effect to find. The only large, high-quality studies that have reported an improvement in mortality

TABLE 3.
Estimated Effect of Early Corticosteroid Therapy on Primary Outcomes

	Adjusted OR (95% CI)	Adjusted Effect (95% CI)	*p*
Outcomes ($n = 352$)			
Vasoactive-inotropic support-free days		0.72 (—0.85 to 2.29)	0.370
Duration of vasoactive-inotropic support[a]		—0.37 (—1.47 to 0.72)	0.503
Survival to month 1 without new morbidity[b,c]	1.37 (0.83–2.28)		0.218
Survival to month 1	1.46 (0.62–3.60)		0.387
New morbidity[a]	0.70 (0.39–1.23)		0.218
Outcomes (HRQL cohort, $n = 229$)			
PSD[d] of HRQL or mortality at month 1	0.70 (0.40–1.23)		0.212
Mortality at month 1	0.63 (0.25–1.50)		0.298
PSD of HRQL among month-1 survivors	0.74 (0.38–1.41)		0.360

HRQL = health-related quality of life, OR = odds ratio, PSD = persistent, severe deterioration.
[a]Among month-1 survivors.
[b]Month 1 refers to 21–42 calendar days following the hospital admission.
[c]There were four subjects missing Functional Status Score (FSS) at day 28 or hospital discharge. New morbidity was defined as a worsening in FSS by 3 or more points from baseline to hospital discharge or day 28, whichever came first.
[d]PSD, persistent, severe deterioration of HRQL below baseline, specifically, HRQL scores (Pediatric Quality of Life Inventory or Functional Status version II-R [FSII-R]) persisting >25% below the baseline HRQL.
Models were weighted using stabilized inverse probability of treatment weights. Additionally, all models control for Pediatric Risk of Mortality III and site I.

TABLE 4.
Estimated Effect of Early Corticosteroid Therapy on Secondary Outcomes

Outcomes ($n = 352$)	Adjusted Effect (95% CI)	p
PICU-free days	−0.21 (−1.87 to 1.44)	0.799
Hospital-free days	−1.48 (−3.34 to 0.37)	0.117
Sum of Pediatric Logistic Organ Dysfunction-2	−8.68 (−22.01 to 4.64)	0.201
Ventilator-free days	1.14 (−0.70 to 2.97)	0.223

Models were weighted using stabilized inverse probability of treatment weights. Additionally, all models control for Pediatric Risk of Mortality III and site I.

attributable to corticosteroids are adult-based, but these results are not reliably reproducible (34–36, 40). Our results are similar to other observational cohort studies that have either demonstrated harm or failed to show a benefit of adjunctive corticosteroid therapy in children with septic shock (2, 8–11, 14). Several of these studies were not able to account for illness severity at PICU admission to the extent we were able to do with our propensity score-weighting approach.

The findings of this study are significant for a number of reasons. First, they add to the literature regarding the use of early adjunctive corticosteroids in septic shock. Despite a wealth of randomized control trials, observational cohort studies, and meta-analyses, there remains significant controversy regarding corticosteroid use for sepsis within the medical community. This debate persists for a number of reasons. Studies that examine the effect of corticosteroids in patients with septic shock are notoriously heterogeneous in terms of patient population (degree of shock, etiology of sepsis, underlying medical conditions, etc.) and treatment regimen, making it difficult to draw a unified conclusion regarding the effectiveness of adjunctive corticosteroid therapy in these patients. Additionally, given the low rate of mortality of pediatric septic shock in resource-rich nations, an interventional trial that is adequately powered to evaluate the effect of early corticosteroid therapy on mortality would require significant resources, time, equipoise, and large-scale collaboration because of the need to enroll thousands of research subjects.

Second, we demonstrate that adjunctive corticosteroids continue to be commonly administered to pediatric patients with septic shock. In this cohort, 155 of 352 of patients (44%) received either hydrocortisone or methylprednisolone on study day 0 or 1. In the entire cohort ($n = 352$), 229 patients (65%) received at least one systemic steroid (methylprednisolone, hydrocortisone, dexamethasone, and prednisone/prednisolone) during their PICU stay. This frequency of corticosteroid usage, despite inadequate evidence of benefit, is similar to previous studies (2, 8–11) and reinforces the need for high-quality data from a randomized controlled trial in children.

Third, our analysis focuses on clinically meaningful outcomes, such as survival without new morbidity and HRQL as primary outcomes. The results from the LAPSE trial revealed that although 9% of the cohort suffered inhospital mortality, 35% of survivors suffered a significant deterioration in their HRQL that persisted at least 1 year following their hospitalization (5). Although we were unable to demonstrate a difference in HRQL outcomes among those treated with early corticosteroid therapy, the profound, persistent burden of morbidity in these patients warrants further investigation to reveal how these outcomes are affected by any current or future therapies.

Fourth, our statistical approach likely provided more precise estimates of the effect of early corticosteroid therapy on patient outcomes than previous studies. By using a propensity score modeling approach, we were able to account for a larger number of clinical institutions and illness severity measures at PICU admission without compromising model integrity. Our results derive from a sizable cohort of 352 patients admitted to 12 different pediatric hospitals across the United States.

This study has important limitations. First, the LAPSE investigation was not primarily designed to detect or evaluate the risks or benefits of early corticosteroid therapy. The potential adverse effects of corticosteroids were not systematically recorded. Time of first corticosteroid administration was not recorded, which limited the ability to narrow the treatment window. Limiting the treatment window to day 0 may have wrongly categorized patients admitted close to midnight, even if corticosteroids were prescribed within the first few hours of admission. This is a limitation of our study. Second, our study included methylprednisolone in the treatment definition. We recognize that hydrocortisone is the only steroid with any evidence to support its use in septic shock. However, given

the prevalence, dose, and pharmacologic properties of methylprednisolone administration during the treatment window in this cohort, these patients were included in the treatment group. Excluding patients who received methylprednisolone in the treatment window would ignore a sizeable subcohort subjected to most of the same corticosteroid effects as the subcohort who received hydrocortisone. Additionally, we could not ascertain the indication for methylprednisolone use in this cohort. This is a significant limitation of our study. Thus, a sensitivity analysis was performed in which the patients receiving only methylprednisolone on day 0 or 1 were placed in the "No Early Corticosteroid" group. There remained no significant difference in any of the outcomes associated with early corticosteroid (hydrocortisone) therapy. The duration of corticosteroid use has the potential to affect the outcomes of interest. However, we were unable to stratify results based on duration of steroid use with our approach. Third, it is unclear how corticosteroids administered outside of the study definition of early corticosteroid therapy, such as dexamethasone or systemic steroids initiated after study day 1, affected outcomes. Fourth, although our imputation calculation did not suggest significant bias due to missing HRQL data at month 1, potential bias due to loss of follow-up remains. Fifth, it is possible that the confounding variables identified for the propensity analysis were incomplete.

Although this study adds to the body of literature surrounding the use of corticosteroids in pediatric sepsis, a high-quality randomized control trial is needed to fully address this issue. Currently enrolling, the Stress Hydrocortisone in Pediatric Septic Shock (NCT03401398) trial is a large (enrollment target $n = 1034$), double-blinded, randomized controlled trial that will examine the potential benefits and risks of adjunctive hydrocortisone therapy in children with fluid and vasoactive-inotropic refractory septic shock. Until the results of this study are available, providers should continue to use corticosteroids with caution given the lack of clear benefit.

CONCLUSIONS

This study examined the association of early adjunctive corticosteroid therapy with mortality and HRQL outcomes among children with septic shock. After adjusting for variables with the potential to confound the relationship between early corticosteroid therapy and clinically meaningful endpoints, there was no association of improved outcomes with this therapy. Results from this propensity analysis provide additional justification for equipoise regarding corticosteroid therapy for pediatric septic shock and ascertain the need for a well-designed clinical trial that will rigorously examine benefit/risk for this intervention.

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