Cumulative Corticosteroid Exposure and Infection Risk After Complex Pediatric Cardiac Surgery

Christopher W. Mastropietro, MD, Renee Barrett, MD, Maria Caridad Davalos, MD, Marwan Zidan, PhD, Kevin M. Valentine, MD, Ralph E. Delius, MD, and Henry L. Walters, III, MD

Department of Pediatrics, Division of Critical Care, and Departments of Pediatrics and Cardiovascular Surgery, Wayne State University, Children's Hospital of Michigan, Detroit, Michigan

Background. **Children undergoing cardiac surgery may receive corticosteroids preoperatively to temper cardiopulmonary bypass-related inflammation, postoperatively for hemodynamic instability, and periextubation to reduce airway edema. Recent data have associated preoperative corticosteroids with infection. We aimed to determine if there is a relationship between cumulative corticosteroid exposure and infection.**

Methods. **A retrospective review of children who underwent cardiac surgery at our institution from January 2009 to July 2010 was performed. To limit study heterogeneity, patients who were 5 years or younger with basic Aristotle score of 7 or higher and intensive care unit stay of 7 days or more were included. Infections during the first 30 postoperative days were recorded, defined as clinically relevant positive blood, urine, respiratory, or wound cultures, or culture-negative sepsis treated with 7 or more days of antimicrobial therapy. Multivariate logistic regression analysis was performed to determine independent risk factors for infection.**

Results. **Seventy-six patients were reviewed. All patients received intraoperative methylprednisolone, 48% received postoperative hydrocortisone, and 86% received periextubation dexamethasone. Twenty-six patients (36%) had 58 infections. On univariate analysis, patients with infection had greater median comprehensive Aristotle score (14.5 [intraquartile range (IQR): 12.5 to 16] versus 11.5 [IQR: 10 to 13.1], $p = 0.001$), maximum vasoactive inotrope score (29 [IQR: 24 to 40] versus 24 [IQR: 17 to 31], $p = 0.031$, days endotracheally intubated (12 [IQR: 7 to 30] versus 5 [IQR: 4 to 6.5], $p < 0.001$), and days of corticosteroid exposure (7 [IQR: 5 to 12] versus 4 [IQR: 2 to 5), $p < 0.001$). Also, patients with infections more often underwent delayed sternal closure ($p = 0.008$). On multivariate analysis, days endotracheally intubated ($p = 0.023$) and days of corticosteroid exposure ($p = 0.015$) remained significant.**

Conclusions. **For children undergoing complex cardiac surgery, greater cumulative duration of corticosteroid exposure is independently associated with postoperative infection.**

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Corticosteroids use in children undergoing cardiac surgery has become relatively commonplace. There is a considerable body of literature focusing on the use of corticosteroids preoperatively in an attempt to temper the potentially detrimental effects of cardiopulmonary bypass-related inflammation [1–10]. Several centers have also described the use of hydrocortisone postoperatively to improve hemodynamics in infants and children with low cardiac output and hypotension [11–13]. Other centers have reported a benefit from the use of periextubation dexamethasone to prevent postextubation upper airway obstruction [14]. At many institutions, including our own, all three of these practices occur. In other words, children undergoing cardiac surgery, especially those with complex lesions and prolonged postoperative courses, can potentially be exposed to numerous doses of corticosteroids throughout their hospital stay.

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Address correspondence to Dr Mastropietro, Wayne State University, Children's Hospital of Michigan, Carl's Bldg, 4th Flr, 3901 Beaubien St, Detroit, MI 48201; e-mail: cmastrop@med.wayne.edu.

The benefits of corticosteroids in these clinical scenarios are not clear. The two largest studies to date of preoperative and perioperative corticosteroid use using the Pediatric Health Information Systems and Society of Thoracic Surgeons Congenital Heart Surgery Databases failed to demonstrate improved outcomes [7, 8]. Conversely, these two studies reported an association between corticosteroid use and postoperative infections. Based on these data, we aimed to determine if postoperative infections were more frequent as cumulative duration of corticosteroid exposure increased in children recovering from complex cardiac surgery at our institution. We hypothesized that patients who received multiple courses of corticosteroids would therefore be more likely to have postoperative infections.

Patients and Methods

Study Population

This study was a retrospective chart review approved by the Institutional Review Boards at Wayne State University and the Detroit Medical Center. Inclusion

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criteria for the study were the following: age 5 years or younger, basic Aristotle complexity score of 7 or greater [15], and pediatric intensive care unit (ICU) length of stay of 7 days or longer. The inclusion criteria were chosen to limit study heterogeneity by focusing the study on our most complicated patients, those with complex surgeries and prolonged pediatric ICU courses who are at greatest risk of postoperative infection [16–18].

Operative and Postoperative Management

All patients received intraoperative methylprednisolone 30 mg/kg before surgical incision. Cardiopulmonary bypass was performed using a Terumo System One heart-lung machine with a roller arterial pump (Terumo Cardiovascular Systems, Ann Arbor, MI); a Capiox RX-05 or Capiox RX15 oxygenator (Terumo Cardiovascular Systems), depending on body surface area; and a Jostra HCU-30 heater-cooler unit (Maquet Cardiopulmonary, Solna, Sweden). Cardiopulmonary bypass was instituted with target flow rate of 2.5 to 3.0 $L \cdot min^{-1} \cdot m^{-2}$. Acid-base status was managed using a pH stat blood gas strategy. After cross-clamp removal, zero balanced ultrafiltration was started. Twenty minutes of modified ultrafiltration was initiated after terminating cardiopulmonary bypass.

Postoperatively, patients received intravenous fluids for daily maintenance fluid and electrolyte requirements, packed red blood cells to maintain hematocrit greater than 30%, fresh frozen plasma and platelets as needed to reverse postsurgical coagulopathy, 5% albumin administration for additional fluid resuscitation as deemed necessary by the ICU team, and prophylactic cefazolin while thoracostomy tubes were in place. The decision to provide intravenous hydrocortisone 1 mg/kg every 6 hours for hemodynamic instability was also at the subjective discretion of the ICU team.

Patients returned to the ICU on synchronized intermittent mandatory ventilation. Initial ventilation index was calculated in the following manner [19]: ventilation index = [RR × (PIP − PEEP × $PaCO_2$] / 1,000, where RR is respiratory rate, PIP is peak inspiratory pressure, and PEEP is positive end-expiratory pressure. Patients were extubated from ventilator support if they were breathing comfortably with good gas exchange on the following settings: RR 5 or fewer breaths per minute, pressure support 10 cmH_2O or less, PEEP 5 cmH_2O or less, and fraction of inspired oxygen concentration 0.4 or less. Periextubation intravenous dexamethasone 0.5 mg/kg every 6 hours was provided to patients deemed at risk for postextubation upper airway obstruction, which was the majority of the study population (ie, infants and small children with prolonged postoperative endotracheal intubation).

Data Analysis

Demographic, anthropometric, perioperative, and postoperative data were recorded for all patients. Descriptive statistics were used to describe the study groups. Data are represented as median with intraquartile range (IQR) for continuous variables and counts with percentages for categorical variables unless otherwise noted. These data include the comprehensive Aristotle score, which is designed as a complexity adjustment tool to be used in outcome analyses in pediatric cardiac surgery [15]. The score accounts for preoperative comorbidities (eg, mechanical ventilation, genetic abnormalities, and so forth) and procedure-specific and anatomic variability between lesions. Most importantly, the score has been shown to be a significant predictor of postoperative morbidity and mortality [20, 21]. Maximum vasoactive inotrope score (VIS) during the first 48 postoperative hours was also determined for all patients. The vasoactive inotrope score was calculated using the following formula: (dopamine + dobutamine + [milrinone × 10] + [epinephrine × 100] + [norepinephrine × 100] + [vasopressin × 10,000]). Maximum vasoactive inotrope score during the first 48 postoperative hours has also been shown to be a significant predictor of outcome after pediatric cardiac surgery, more so than other measures of postoperative disease acuity such as Pediatric Risk of Mortality (PRISM) III score and the presence of low cardiac output syndrome [22, 23].

Infections during the first 30 postoperative days were recorded. This timeframe was chosen because it is a standard used in the definition of postoperative infection [7, 24]. Infection was defined as clinically relevant positive blood, urine, respiratory, or wound cultures, or culture-negative sepsis (ie, systemic inflammatory response syndrome with suspected infection) treated with 7 days or more of antimicrobial therapy. This latter definition has been used previously [7]. Data from patients with postoperative infections were compared with those from patients without infection using Mann-Whitney U tests for continuous variables and χ^2 or Fisher exact tests for categorical variables. Because the study focused on infections during the first 30 postoperative days, only days of corticosteroid exposure, days endotracheally intubated, and ICU days during the first 30 postoperative days were included in the comparisons. Days of corticosteroid exposure were defined as distinct 24 hours periods during which at least one dose of systemic corticosteroids was administered. Multivariate logistic regression analysis was performed to determine independent risk factors for postoperative infection. Odds ratios (OR) with 95% confidence intervals (CI) were calculated for each variable included in the multivariate model. All statistical calculations were performed using IBM SPSS, version 19 (SPSS, Chicago, IL).

Results

Seventy-six patients who met inclusion criteria were identified. Twenty-seven patients (36%) had 58 infections during the first 30 postoperative days, with a median of 2 infections per patient (range, 1 to 4). The median postoperative day of first infection in these patients was day 7 (IQR: 3 to 13; range, 1 - 27). The sites of infection are listed in Table 1. The most common site of infection was the respiratory tract, which includes ventilator-associated tracheobronchitis and pneumonia. The most

Table 1. Frequency of Infections per Site

Infection Site	Frequency
Respiratory tract	26 (44.8%)
Culture-negative sepsis	11 (19%)
Urinary tract	10 (17.2%)
Bloodstream	7 (12.1%)
Wound/mediastinum	2 (3.4%)
Pleural fluid	1 (1.7%)
Gastrointestinal tract	1 (1.7%)

common pathogens were *Enterobacter cloacae* (5 respiratory infections, 1 urinary tract infection), *Staphylococcus aureus* (3 respiratory, 1 blood, 1 pleural fluid, 1 wound), and *Candida albicans* (5 urinary tract infections). Other pathogens, in order of decreasing frequency, included *Staphylococcus epidermidis*, *Pseudomonas aeruginosa*, *Serratia marsescens*, *Enterococcus faecalis*, *Influenza A*, *Klebsiella pneumonia*, *Escherichia coli*, *Stenotrophomonas maltophilia*, *Citrobacter freundii*, *Streptococcus pneumoniae*, *Moraxella catarhalis*, *Hemophilus influenza*, and *Clostridium difficile*. Demographic, anthropometric, and perioperative data for those patients with and without postoperative infections are provided in Table 2 and Table 3. Table 3 provides a list of surgical procedure performed, stratified based on basic Aristotle complexity level. Surgical complexity as represented by the basic Aristotle score was not statistically different between groups, but comprehensive Aristotle score [15], which takes into account known risk factors for postoperative infection such as preoperative hospitalization, preoperative mechanical ventilation, and genetic abnormalities [16, 17], was significantly higher in patients with infection, 14.5 (IQR: 12.5 to 16) versus 11.5 (IQR: 10 to 13.2; $p = 0.001$).

Table 2. Demographic, Anthropometric, and Perioperative Data

Variable	Infection (n = 27)	No Infection (n = 49)	*p* Value
Age, months	2.7 (0.47–9.9)	2.1 (0.37–6)	0.252
Female	11 (41)	22 (45)	0.726
Weight, kg	4 (3.4–7.7)	4.4 (3.2–7.1)	0.952
Basic Aristotle score	9 (8–11)	9 (8–10.3)	0.510
Comprehensive Aristotle score	14.5 (12.5–16)	11.5 (10–13.2)	0.001[a]
Single ventricle anatomy	5 (19)	6 (12)	0.506
Cardiopulmonary bypass time, min	215 (131–278)	198 (146–223)	0.551
Aortic cross-clamp time, min	98 (68–121)	94 (52–140)	0.457
Deep hypothermic circulatory arrest	9 (33)	25 (51)	0.138

[a] Statistical significance $p < 0.05$.

Data are median (interquartile range) for continuous variables and n (%) for categorical variables.

All patients received intraoperative methylprednisolone; 37 (48%) received postoperative hydrocortisone; 68 (89%) received postoperative dexamethasone; 5 patients received postoperative prednisolone or methylprednisolone for postoperative pericardial effusions; and 1 patient received postoperative methylprednisolone as pretreatment for platelet transfusion. Corticosteroid exposure and other postoperative data for those with and without infection are given in Table 4. Patients with infection were more hemodynamically unstable, more likely to have an open chest, and spent more time intubated and in the ICU during the first 30 postoperative days. Days in the ICU after extubation, however, were not statistically different between groups. A multivariate logistic regression analysis incorporating comprehensive Aristotle score, maximum VIS, extracorporeal life support, delayed sternal closure, days of steroid exposure, and days endotracheally intubated was performed. The results are organized in Table 5. Only days of steroid exposure (OR 1.47, 95% CI: 1.08 to 1.99) and days endotracheally intubated (OR 1.27, 95% CI: 1.03 to 1.55) were significantly associated with infection in this cohort of complex cardiac surgical patients. The distribution of days of corticosteroid exposure within each group is illustrated in Figure 1.

Comment

This is the first report of an association between increased cumulative duration of corticosteroid exposure and infection after pediatric cardiac surgery. Specifically, patients in our study who had postoperative infections received a median of 7 days of corticosteroid exposure consisting primarily of intraoperative methylprednisolone and multiple doses of postoperative hydrocortisone or dexamethasone or both. We acknowledge that the patients who became infected had more preoperative comorbidities (ie, greater comprehensive Aristotle score) and were sicker postoperatively (ie, higher inotrope requirements, more likely to have an open sternum). On multivariate logistic regression analysis, however, adjusting for these confounding variables, the association between days of steroid exposure and infection remained significant. Based on these data, more judicious use of corticosteroids in this patient population may be warranted.

Prior reports on the clinical benefits and detriments of perioperative corticosteroids have been conflicting [1–10]. Although recent retrospective data have associated perioperative corticosteroids with postoperative infection and other morbidities, this effect was predominantly seen in the less complex patients [7, 8]. Indeed, Clarizia and colleagues [9] recently reported retrospective data demonstrating beneficial clinical effects of perioperative methylprednisolone in complex pediatric cardiac surgical patients, defined as having a comprehensive Aristotle score of 10 or greater [9]. The dosing range used in this study was methylprednisolone 30 to 50 mg/kg, depending on whether patients received one, two, or

Table 3. Primary Procedures Performed Organized by Basic Aristotle Complexity Level

Aristotle Complexity Level	Cardiac Procedure Performed	Infection (n = 27)	No Infection (n = 49)
Level 2	Complex VSD repair	1	0
Basic score 7.0–7.9	Aortic arch repair	0	2
	LVAD placement for DCM	1	1
	PA angioplasty, B-T shunt	1	3
	Tricuspid valve replacement	0	1
	Supravalvar aortic stenosis	0	1
	TOF/RVOTO repair	2	3
Level 3	Aortic arch reconstruction	0	2
Basic score 8.0–9.9	Complete AVSD repair	3	4
	Hemi-Fontan/Fontan	4	2
	Right atrial tunnel repair	0	1
	TOF/RVOTO repair	2	4
	TAPVR repair	2	2
	TV closure, atrioplasty, B-T shunt	0	1
Level 4	ALCAPA repair	1	0
Basic score 10–15	Aortic arch reconstruction w/VSD repair	0	3
	Complex TOF repair	3	2
	D-TGA s/p arterial switch	3	11
	Left ventricle to PA conduit for L-TGA	0	1
	Norwood or DKS procedure	3	2
	Truncus arteriosus repair	1	3

ALCAPA = anomalous left coronary artery from pulmonary artery; AVSD = atrioventricular septal defect; B-T = Blalock-Taussig; DCM = dilated cardiomyopathy; DKS = Damus-Kaye-Stansel; D-TGA = D-transposition of great arteries; L-TGA = L-transposition of great arteries; LVAD = left ventricular assist device; PA = pulmonary atresia; RVOTO = right ventricular outflow tract obstruction; TAPVR = total anomalous pulmonary venous return; TOF = tetralogy of Fallot; TV = tricuspid valve; VSD = ventricular septal defect.

three perioperative doses. Further, perioperative corticosteroids were not associated with a higher odds of infection as compared with controls; no mention was made of postoperative corticosteroid use. Hence, convincing data associating perioperative corticosteroids alone with infection in complex pediatric cardiac surgical patients are lacking. It is possible that the detrimental effects of corticosteroids on immune function and wound healing are outweighed by their antiinflammatory effects in complex pediatric patients with prolonged exposures to cardiopulmonary bypass but not so in less complex patients with relatively shorter operative courses. Of note, a recent prospective study [10] determined that there was no benefit and possible detriment when using two doses of perioperative steroids as compared with one in a cohort of neonates undergoing pediatric cardiac surgery. Therefore, in regard to perioperative corticosteroids, until more prospective data are available, limiting complex neonates and children to one intraoperative dose may be a reasonable means of decreasing their overall corticosteroid exposure.

To our knowledge, there are no previous data associating postoperative use of corticosteroids for hemodynamic instability with infection in children recovering from cardiac surgery. Corticosteroids administration can lead to rapid increase in β-receptor density by increasing β-receptor messenger RNA expression [25], suppression of nitric oxide synthase [26], and inhibition of nuclear factor kappa B [27] with consequent reductions in proinflammatory cytokines [28]. These are some of the mechanisms by which hydrocortisone can increase blood pressure in children after cardiac surgery, although this effect is not seen in all patients [12]. Relative adrenal insufficiency after cardiopulmonary bypass has been reported to occur in approximately 20% of patients [29], which may explain this observed variable hemodynamic response. In other words, hydrocortisone may not be helpful and therefore not necessary in patients with normal adrenal function. Unfortunately, once initiated, bedside clinicians may be reluctant to discontinue it until hemodynamic stability is achieved, at which point it must be weaned to prevent adrenal crisis and patients get exposed to additional days of corticosteroids. This scenario occurred in many of our patients. Identification of children with relative adrenal insufficiency after cardiac surgery may be another means of limiting corticosteroid exposure. Low random cortisol concentrations have been shown not to be predictive of response to hydrocortisone therapy [12] and not to correlate with inotropic support or postoperative fluid resuscitation in children recovering from cardiac surgery [29, 30]. Consequently, random cortisol concentrations are not reliable markers of postoperative adrenal function. Conversely, relative adrenal insufficiency in children recovering from cardiac surgery as defined by an increase in total cortisol less than 9 mg/dL from baseline after low-dose corticotropin stimulation test has been associated with higher requirements for inotropic support and fluid resuscitation [29, 30]. Low-dose corticotropin stimulation

Table 4. Postoperative Data

Variable	Infection (n = 27)	No Infection (n = 49)	*p* Value
Open chest	12 (44%)	8 (14%)	0.008[a]
ECMO	5 (19%)	4 (5%)	0.124
Initial ventilation index	20.8 (14.8–24.3)	19.6 (14.8–23.5)	0.684
PRISM III score[b]	9 (5–13)	8 (5–12)	0.703
Maximum VIS[b]	28.5 (23.5–40)	23.5 (16.8–30.8)	0.031[a]
Peak lactate, mg/dL	5.1 (2.3–6.8)	4.0 (1.7–5.7)	0.345
Fluid input,[c] mL/kg	376 (293–622)	406 (317–539)	0.926
Fluid balance,[c] mL/kg	−17 (−61 to 18)	−19 (−67 to 31)	0.832
Inhaled nitric oxide	13 (48%)	22 (45%)	0.786
Days of steroid exposure[d]	7 (5–12)	4 (2–5)	< 0.001[a]
Hydrocortisone dose, mg/kg	0 (0–17.6)	18 (0–23.9)	0.003[a]
Dexamethasone dose, mg/kg	3.5 (2–6)	2.1 (1.7–3.8)	0.026[a]
Ventilator days[d]	12 (7–30)	5 (4–6.5)	< 0.001[a]
ICU days[d]	29 (13–30)	11 (9–15)	< 0.001[a]
ICU, ventilator days[e]	6 (0–13)	7 (4–9.5)	0.259
Mortality	6 (22%)	3 (6%)	0.061

[a] Statistical significance $p < 0.05$. [b] During first 48 hours. [c] During first 72 postoperative hours. [d] Days during the first 30 postoperative days. [e] Days in intensive care unit (ICU) after extubation during the first 30 postoperative days.

Data are mean (SD) for normal continuous variables, median (range) for skewed continuous variables, and n (%) for categorical variables.

ECMO = extracorporeal membrane oxygenation; PRISM = Pediatric Risk of Mortality; VIS = vasoactive inotrope score.

tests could practically be performed upon patient arrival to the intensive care unit, quickly identifying optimal candidates for postoperative hydrocortisone. Bedside clinicians could then have a low threshold for postoperative hydrocortisone use in these patients and a high threshold in others.

Data on the use of periextubation dexamethasone in children are also conflicting [14]. Studies that demonstrate the greatest benefit to this practice include patients with underlying airway anomalies who by definition have higher risk of postextubation airway complications. The incidence of reintubation for postextubation in critically ill children is quite low at 0.9% to 1.9% [31–33], making it difficult to identify risk factors for this postoperative complication. Data on the incidence of postextubation stridor and distress secondary to upper airway obstruction without reintubation in pediatric cardiac surgical patients have not been reported. Retrospective and prospective studies attempting to identify risk factors for this latter complication could be helpful in further limiting corticosteroid exposure in these patients.

Our study has several limitations. As noted above, patients who had infections were more ill. To appropriately adjust for these differences, we have included all of the risk factors recently identified by The Society of Thoracic Surgeons Congenital Heart Surgery

Table 5. Multivariate Logistic Regression Analysis of Risk Factors for Postoperative Infection

Variable	Odds Ratio	95% CI	*p* Value
Comprehensive Aristotle score	1.17	0.97–1.48	0.205
Maximum vasoactive inotrope score	1.03	0.97–1.09	0.332
Open chest	1.17	0.17–7.84	0.874
ECMO	3.26	0.15–69.6	0.449
Days endotracheally intubated	1.27	1.03–1.55	0.023[a]
Days of steroid exposure	1.47	1.08–1.99	0.015[a]

[a] Statistical significance $p < 0.05$.

CI = confidence interval; ECMO = extracorporeal membrane oxygenation.

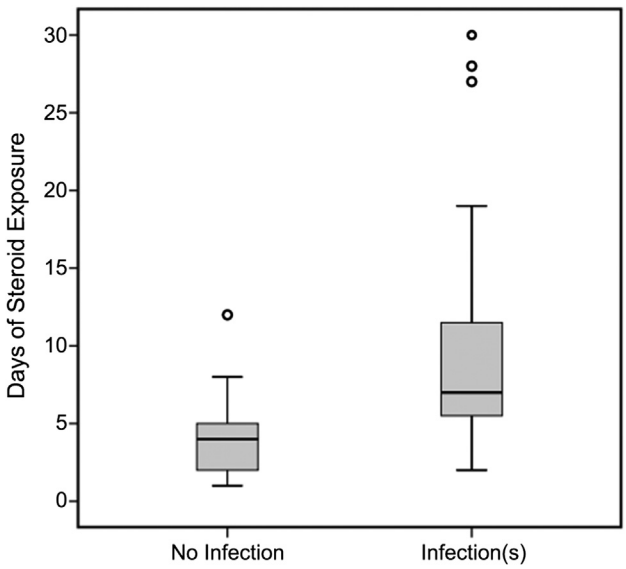

Fig 1. The distribution of days of corticosteroid infection for patients with and patients without postoperative infection, p less than 0.001 on univariate analysis.

Database to be most strongly associated with infection [16, 17] and validated disease severity scores into our multivariate analysis. Nevertheless, there may be other immeasurable risk factors that could have influenced our results, for example, variations in nursing care, genetic polymorphisms, and so forth. Although patients with infections did receive higher cumulative doses of both hydrocortisone and dexamethasone postoperatively, we did not compare the cumulative dose of all corticosteroids received because the differences in the relative immunosuppressive potencies of each drug are difficult to accurately quantitate. Therefore, we were only able to establish an association between cumulative duration of immunosuppression due to corticosteroid exposure, not cumulative dose of corticosteroids. It is arguable that the duration of corticosteroid exposure may be more important than the cumulative dose in many of these patients with protracted postoperative courses. Further, most but not all days of corticosteroid exposure and mechanical ventilation occurred before the initiation of antibiotic therapy for the postoperative infections. Retrospectively identifying the precise onset of infection in patients is difficult, especially in patients with multiple infections. We therefore opted to include all days of steroid exposure and mechanical ventilation into our analysis, even those few days of exposure that might have occurred after the onset of the patients' infections. Consequently, the extended courses of steroid exposure used in some patients in our study could simply represent a marker of disease severity rather than a risk factor for infection. Additionally, we focused the study on our most complex patients with prolonged ICU stays. Our results are therefore not generalizable to patients with less complex anatomy or shorter ICU exposure. Future studies in these patient populations might be revealing, although the number of patients studied would need to be much larger given their low incidence of infection. Lastly, this study represents data from a single center, which may limit their generalizability to other centers.

Despite these limitations, and until more data are available, we hope our results along with prior reports linking corticosteroids with postoperative infection [7, 8] will foster a more conservative approach to their use in children recovering from pediatric cardiac surgery.

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