Intensive Care Med (2015) 41:1658–1666
DOI 10.1007/s00134-015-3953-4

ORIGINAL

Nadir Yehya
Sabah Servaes
Neal J. Thomas
Vinay M. Nadkarni
Vijay Srinivasan

Corticosteroid exposure in pediatric acute respiratory distress syndrome

Received: 11 May 2015
Accepted: 26 June 2015
Published online: 10 July 2015

Take-home message: Pediatric ARDS patients are commonly exposed to corticosteroids, despite a lack of evidence for their efficacy. In a large, contemporary, prospective pediatric ARDS cohort, corticosteroid exposure >24 h was common (60 %) and was associated with fewer ventilator-free days and longer duration of mechanical ventilation in survivors; these results persisted after multivariate and propensity score adjustment.

Electronic supplementary material
The online version of this article (doi:10.1007/s00134-015-3953-4) contains supplementary material, which is available to authorized users.

N. Yehya (✉) · V. M. Nadkarni · V. Srinivasan
Department of Anesthesiology and Critical Care Medicine, Children's Hospital of Philadelphia and University of Pennsylvania, Suite 7C-26, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104, USA
e-mail: yehyan@email.chop.edu

S. Servaes
Department of Radiology, Children's Hospital of Philadelphia and University of Pennsylvania, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104, USA

N. J. Thomas
Division of Pediatric Critical Care Medicine, Department of Pediatrics and Public Health Science, Penn State Hershey Children's Hospital, 500 University Drive, Hershey, PA 17033, USA

Abstract *Purpose:* Use of systemic corticosteroids in acute respiratory distress syndrome (ARDS) remains controversial, and studies in children are lacking. *Methods:* We performed an observational, single-center study in a prospectively enrolled cohort of children meeting criteria for ARDS (both Berlin 2012 and AECC 1994 acute lung injury) and pediatric ARDS (PARDS, as defined by PALICC 2015). Comprehensive analysis of corticosteroid utilization was planned, and detailed information collected on corticosteroid use, timing, treatment duration, and cumulative dose while mechanically ventilated. We assessed the association between corticosteroid exposure >24 h and outcomes. *Results:* Of the 283 children with PARDS (37 deaths, 13 %), 169 (60 %) received corticosteroids for >24 h while ventilated: 51 % hydrocortisone, 41 % methylprednisolone, 5 % dexamethasone, 3 % combination of corticosteroids. Corticosteroid exposure >24 h was associated with increased mortality, fewer ventilator-free days at 28 days (VFD), and longer duration of ventilation in survivors in unadjusted analyses (all $p < 0.05$). Multivariate and propensity score adjusted analyses confirmed independent association of corticosteroid exposure with fewer VFD and longer duration of ventilation in survivors, but not with mortality. In planned analyses of high-risk subgroups, no benefit was seen with corticosteroids exposure, with fewer VFD associated with corticosteroid exposure >24 h in patients with ≥3 organ failures and immunocompromised patients. *Conclusions:* Corticosteroid exposure >24 h was independently associated with fewer VFD and longer duration of ventilation in survivors, even after adjustment for key potential confounders, including severity of illness, oxygenation index, immunocompromised status, and number of organ failures.

Keywords Pediatric · Acute respiratory distress syndrome · ARDS · PARDS · Children · Corticosteroids

Introduction

The role of corticosteroids in acute respiratory distress syndrome (ARDS) remains controversial. Clinical trials [1–4], observational studies [5–7], and meta-analyses [8] do not consistently suggest improved outcomes, and concerns for immunosuppression [9], secondary infections [6], and neuromyopathy [2] have prompted efforts to better elucidate the role for corticosteroids in ARDS.

Children with ARDS are often treated on the basis of evidence extrapolated from adult studies, despite having distinct epidemiology and outcomes [10–16]. Recently, the Pediatric Acute Lung Injury Consensus Conference (PALICC) convened to develop definitions of pediatric ARDS (PARDS) [17]. Children with PARDS are often exposed to corticosteroids, with estimates of exposure rates ranging from 20 to 60 % in published cohorts [12, 16, 18]. On the basis of a paucity of data and equipoise regarding corticosteroids in adult ARDS, PALICC recommended further study focusing on use of corticosteroids in PARDS [17].

Recently, we described a prospective study of PARDS involving 283 children [16] aiming to identify variables associated with survival and ventilator-free days (VFD). Corticosteroid use was identified a priori as a variable of interest, and detailed information on corticosteroid use, type, dosage, and duration collected. The present study tested the association between corticosteroid exposure and outcomes in a large cohort of children with PARDS.

Methods

Patient selection

This prospective, observational study was approved by the Children's Hospital of Philadelphia's (CHOP) Institutional Review Board, and requirement for informed consent waived. The cohort has been previously described [16]. Consecutive patients in the pediatric intensive care unit (PICU) were screened between 1 July 2011 and 30 June 2014. We included children (>1 month and <18 - years) undergoing invasive mechanical ventilation meeting American-European Consensus Conference criteria for ALI ($Pao_2/Fio_2 \leq 300$ on two consecutive arterial blood gases separated by at least 1 h and bilateral parenchymal infiltrates). Exclusion criteria were (1) respiratory failure from cardiac failure or fluid overload, (2) exacerbation of chronic respiratory disease, (3) chronic ventilator dependence, (4) cyanotic heart disease, (5) mechanical ventilation for >7 days before $Pao_2/Fio_2 \leq 300$, and (6) established ALI prior to transfer to CHOP PICU. Determination of bilateral infiltrates was made independently by a PICU attending physician and a pediatric radiologist masked to clinical data; only cases agreed to by both as consistent with ALI met inclusion. Determination of hydrostatic pulmonary edema (from either heart failure or anuric/oliguric renal failure) as the sole etiology of respiratory failure was made in consultation with the PICU attending using available data. While this study was initiated prior to publication of the 2012 Berlin definition of ARDS [19], all enrolled patients were invasively ventilated with positive end-expiratory pressure (PEEP) ≥ 5 cmH_2O, and therefore met Berlin criteria for ARDS. Similarly, all patients met 2015 PALICC oxygenation index (OI) criteria for PARDS [17].

PARDS management

Demographics, ventilator settings, and laboratory data were recorded for the first 3 days of PARDS. In the absence of a standardized ventilator protocol, our institutional practice is to initiate conventional ventilation with a minimum 5 cmH_2O of PEEP, and attempt to wean Fio_2 to ≤ 0.60. There is no specific target Pao_2, but typically $Pao_2 \geq 60$ mmHg is accepted as long as there is clinical stability. Inability to wean Fio_2 prompts PEEP escalation and subsequent efforts to wean Fio_2, attempting to maintain peak inspiratory pressures (PIP) ≤ 35 cmH_2O. We predominantly utilize decelerating flow during conventional ventilation (either pressure control or pressure-regulated volume control). Persistently elevated PIP (≥ 35 cmH_2O), hypercarbia ($Paco_2 \geq 80$), or inability to wean $Fio_2 \leq 0.60$ despite increasing PEEP prompt consideration for changing ventilator modes, or escalation to extracorporeal membrane oxygenation (ECMO). There is no standardization of ancillary therapies (inhaled nitric oxide, surfactant, neuromuscular blockade, prone positioning, corticosteroids), which is left to the discretion of the PICU attending.

Definition of corticosteroid exposure

We collected extensive information regarding corticosteroid exposure. Type of corticosteroid, timing of initiation, duration of corticosteroid exposure while ventilated, and cumulative corticosteroid exposure during ventilation (expressed as methylprednisolone equivalents, MPE [20]) were recorded. Actual doses administered were verified by reconciliation with nursing medication administration record. Patients were dichotomized to those receiving no or $\leq$24 h of corticosteroids and those receiving >24 h, with the purpose of grouping patients with brief exposures to "stress dose" hydrocortisone (which were rapidly discontinued) and peri-extubation doses of corticosteroids together with those receiving no corticosteroids. Significant corticosteroid exposure was defined as those receiving >24 h of any corticosteroid formulation, consistent with previous reports [21, 22].

Equations

Oxygenation metrics utilized were Pao_2/Fio_2 and OI [(mean airway pressure × Fio_2 × 100)/Pao_2]. The vasopressor score [23] was dopamine (μg/kg/min) × 1 + dobutamine (μg/kg/min) × 1 + epinephrine (μg/kg/min) × 100 + norepinephrine (μg/kg/min) × 100 + phenylephrine (μg/kg/min) × 100 + milrinone (μg/kg/min) × 10. Non-pulmonary organ failures at time of PARDS diagnosis were identified using standard definitions for children [24]. The designation of "immunocompromised" required presence of an immunocompromising diagnosis (oncologic, immunologic, rheumatologic, or transplant) and active immunosuppressive chemotherapy, or a congenital immunodeficiency [25, 26]. Severity of illness score used was the Pediatric Risk of Mortality (PRISM) III at 12 h.

Definitions of outcomes

Reported outcomes are PICU mortality, VFD at 28 days, duration of ventilation in survivors, and PICU-acquired infections. All reference to "mechanical ventilation" implies invasive ventilation, and non-invasive support was not counted toward VFD or total ventilator days. For VFD and duration of mechanical ventilation, the first day was initiation of invasive ventilation. Liberation from invasive ventilation for >24 h defined duration of mechanical ventilation. Patients requiring re-initiation of invasive ventilation after 24 h of extubation had the extra days counted towards total ventilator days. VFD was determined by subtracting total ventilator days from 28 in survivors. All patients with total ventilator days ≥28 days, and all PICU non-survivors were assigned VFD = 0. PICU-acquired infections were based on operational definitions from the Centers for Disease Control and the National Healthcare Safety Network [27], and included central line-associated bloodstream infections, catheter-associated urinary tract infections, ventilator-associated pneumonias, and nosocomial viruses.

Statistical analysis

Data are expressed as percentages or as median [interquartile ranges, IQR]. Most variables were non-normally distributed according to the Shapiro–Wilk test. Differences between distributions of categorical variables were analyzed by Fisher's exact test. Continuous variables were compared using the Kruskal–Wallis test.

Associations between corticosteroid exposure >24 h and outcomes were modeled separately for the independent variables of "corticosteroid exposure >24 h" (dichotomized to yes/no) and for "cumulative corticosteroid dose" (continuous variable, expressed as mg/kg MPE). The dependent outcomes were (1) PICU mortality, (2) VFD, and (3) length of mechanical ventilation in survivors (log-transformed for normalcy). We accounted for confounding using two methods: (1) multivariate adjustment and (2) propensity score adjustment. Like multivariate adjustment, propensity score adjustment attempts to estimate treatment effect after accounting for confounding covariates. The propensity score, which is the predicted probability of a given patient in an observational study receiving an exposure, attempts to balance the observed baseline covariates between the exposed and unexposed cohorts, replicating the balancing of covariates seen in randomized trials.

In the multivariable model, factors associated with the dependent variable (mortality, VFD, or length of mechanical ventilation in survivors) in univariate analysis ($p < 0.1$) were entered into a multivariate regression model. Because multiple ventilator parameters (PIP, Pao_2/Fio_2, OI, use of inhaled nitric oxide) were colinear, only OI was included in the model. In the propensity adjusted model, a propensity score for corticosteroid use >24 h was calculated using the following: age, gender, ethnicity, PRISM III, immunocompromised status, presence of reactive airway disease, cause of PARDS, number of non-pulmonary organ failures, worst OI in the first 24 h, highest vasopressor score in the first 72 h, and cumulative fluid balance in the first 72 h. The propensity scores were divided into quintiles, and the propensity quintile entered as a covariate in the above regression models. For all models (including propensity score derivation), goodness of fit was assessed using Hosmer–Lemeshow statistics. Data were analyzed using Stata 10.0 (StataCorp, LP, College Station, TX).

Results

Characteristics of the PARDS cohort

The cohort is summarized in Table 1. Forty-nine patients received <24 h of corticosteroids (8 single-dose hydrocortisone, 35 peri-extubation dexamethasone, 6 both), and 65 received no corticosteroids. These 114 patients comprised the "corticosteroid exposure ≤24 h" cohort. One hundred and sixty-nine (60 %) children were exposed to corticosteroids >24 h while ventilated. The "corticosteroid exposure >24 h" cohort had higher PRISM III, more immunocompromised patients, higher vasopressor scores, and worse oxygenation (Table 1). Patients with reactive airway disease were more likely to receive corticosteroids >24 h. In unadjusted analysis, the cohort exposed to >24 h of corticosteroid experienced more PICU-acquired infections, longer duration of ventilation, and higher mortality.

Table 1 Characteristics of PARDS cohort

	All patients ($n = 283$)	No corticosteroids or exposure ≤24 h ($n = 114$)	Corticosteroid exposure >24 h ($n = 169$)	p value
Age (years)	4.1 [1.4, 12.8]	4.3 [1.3, 12.9]	4.2 [1.4, 12.3]	0.974
Gender: female (%)	118 (42)	46 (40)	72 (43)	0.706
PRISM III at 12 h	10 [5, 17]	8 [4, 16]	11 [6, 18]	0.050
Immunocompromised (%)	54 (19)	13 (11)	41 (24)	0.007
Reactive airway disease (%)	43 (15)	5 (4)	38 (22)	<0.001
Cause of PARDS				0.111
Infectious pneumonia	164 (58)	58 (51)	106 (63)	
Aspiration pneumonia	28 (10)	13 (11)	15 (9)	
Non-pulmonary sepsis	51 (18)	21 (18)	30 (18)	
Trauma	22 (8)	10 (9)	12 (7)	
Other	18 (6)	12 (11)	6 (3)	
Non-pulmonary organ dysfunctions at PARDS onset	2 [1, 3]	2 [1, 2]	2 [1, 3]	0.518
Serum cortisol (μg/dL) at corticosteroid initiation ($n = 165$)	20.9 [10.2, 32.5]	24.2 [17.6, 32.3]	18.5 [8.3, 32.6]	0.034
Ancillary therapies				
Inhaled nitric oxide	105 (37)	32 (28)	73 (43)	0.010
Neuromuscular blockade	131 (46)	46 (40)	85 (50)	0.100
Prone positioning	5 (2)	0 (0)	5 (3)	0.064
Surfactant	6 (2)	2 (2)	4 (2)	0.726
First 24 h of PARDS				
Worst Pao_2/Fio_2	130 [91, 175]	153 [105, 191]	123 [87, 154]	<0.001
Worst OI	12.2 [8.3, 20.4]	10.6 [7.1, 17.1]	13.6 [9.1, 24.2]	<0.001
First 72 h of PARDS				
Maximum vasopressor score	10 [4, 20]	8 [4, 16]	10 [4, 23]	0.029
Fluid balance (mL/kg)	95 [37, 179]	97 [47, 165]	95 [29, 184]	0.937
Outcomes				
PICU-acquired infections	53 (19)	14 (12)	39 [23]	0.029
Ventilator days (all patients)	10 [6, 17]	8 [6, 15]	11 [7, 19]	0.004
Ventilator days (survivors)	10 [7, 17]	9 [6, 15]	11 [7, 19]	0.013
VFD at 28 days	17 [3, 21]	19 [11, 22]	15 [0, 20]	0.001
PICU deaths (%)	37 (13)	9 (8)	28 (17)	0.034

Among the 160 children receiving >24 h of corticosteroid (Table 2), hydrocortisone and methylprednisolone were the predominant corticosteroids utilized. Corticosteroids were most commonly prescribed on the same day that patients met PARDS criteria, with a median of 0 [IQR 0, 1] days between meeting PARDS criteria and initial corticosteroid administration, and were exposed to a median 8 [4, 20] mg/kg MPE while invasively ventilated. There were no differences between patients exposed to hydrocortisone or methylprednisolone in time to corticosteroid initiation (median 0 days for both, $p = 0.542$), mortality (16 and 17 %, $p = 0.980$), VFD (median 14 [IQR 0, 19] versus 15 [0, 20] days, $p = 0.897$), or duration of ventilation in survivors (median 12 [8, 17] versus 10 [7, 20] days, $p = 0.708$). Because we found no relationship between type of corticosteroid and outcomes, "type of corticosteroid" was not included in subsequent modeling.

Thirty-seven patients (13 %) died in the PICU. In unadjusted analysis, non-survivors had higher PRISM III,

Table 2 Administration of corticosteroids >24 h in 169 patients with PARDS

Corticosteroid administered, n (%)	
Hydrocortisone	87 (51)
Methylprednisolone	69 (41)
Dexamethasone	8 (5)
Combination	5 (3)
At methylprednisolone initiation	
Pao_2/Fio_2	153 [115, 202]
OI	10.3 [7.4, 15.4]
Serum cortisol (μg/dL, $n = 27$)	15.9 [9.9, 32.3]
Vasopressor score	5 [0, 12]
At hydrocortisone initiation	
Pao_2/Fio_2	150 [99, 199]
OI	10.4 [8.3, 18.5]
Serum cortisol (μg/dL, $n = 71$)	18.8 [6.6, 30.4]
Vasopressor score	17 [10, 30]
Initial dose (MPE), mg/kg/day	1 [0.8, 4]
Days after PARDS onset	0 [0, 1]
Duration of therapy (days)	7 [5, 12]
Cumulative dose while invasively ventilated (MPE), mg/kg	8 [4, 20]

Table 3 Variables associated with mortality

Variable	Survived ($n = 246$)	Died ($n = 37$)	Unadjusted odds ratio (95 % CI)	p value
Age (years)	3.9 [1.4, 11.9]	6.9 [2.3, 15.2]	1.06 (1.00–1.12)	0.030
PRISM III at 12 h	9 [5, 15]	20 [12, 30]	1.10 (1.06–1.13)	<0.001
Immunocompromised (%)	35 [14]	19 [51]	6.36 (3.04–13.3)	<0.001
Non-pulmonary organ dysfunctions at PARDS onset	1 [1, 2]	3 [2, 4]	2.84 (2.03–3.98)	<0.001
Worst OI in first 24 h of PARDS	11.4 [7.8, 19.3]	19.6 [10, 29.8]	1.04 (1.02–1.06)	0.001
Maximum vasopressor score in first 72 h of PARDS	8 [3, 18]	15 [7, 26]	1.01 (1.00–1.02)	0.025
Fluid balance in first 72 h of PARDS (mL/kg)	94 [37, 174]	118 [47, 264]	1.003 (1.001–1.006)	0.003
Corticosteroids				
Corticosteroids >24 h	141 (57)	28 (77)	2.32 (1.05–5.12)	0.038
Cumulative dose (mg/kg MPE)	2.4 [0, 10]	5 [0.5, 15.1]	1.02 (1.00–1.03)	0.025

Table 4 Propensity adjusted covariates between patients exposed to ≤24 or >24 h of corticosteroids

Variable	Propensity adjusted odds ratio	95 % CI	p value
Age	1.00	0.96–1.05	0.979
PRISM III	0.99	0.97–1.03	0.936
Immunocompromised (yes)	1.08	0.50–2.34	0.838
Reactive airway disease (yes)	1.34	0.45–4.05	0.600
Non-pulmonary organ dysfunctions at PARDS onset	1.01	0.81–1.25	0.942
Worst OI in first 24 h of PARDS	1.00	0.98–1.03	0.910
Maximum vasopressor score in first 72 h of PARDS	1.00	0.99–1.02	0.734
Fluid balance in first 72 h of PARDS (mL/kg)	1.00	0.99–1.0	0.881

worse oxygenation, higher vasopressor scores, more organ failures, and were more likely to be immunocompromised (Table 3). Both corticosteroid exposure >24 h and cumulative corticosteroid dose were associated with PICU non-survival ($p < 0.05$).

Multivariate adjustment

Multiple regression identified variables independently associated with mortality, VFD, and duration of mechanical ventilation in survivors (Supplementary Tables 1–3). Separate models were constructed using the independent variables "corticosteroid exposure >24 h" (model 1) and "cumulative corticosteroid dose" (model 2). Number of non-pulmonary organ failures and worst OI were independent predictors of poor outcome in every model. Corticosteroid exposure >24 h and cumulative corticosteroid dose were independently associated with VFD and length of mechanical ventilation in survivors, but not mortality.

Propensity score adjustment

To further address potential confounding, a propensity score for corticosteroid exposure >24 h was constructed. The model had an area under the receiver operating characteristic curve of 0.78 (95 % CI 0.73–0.83), suggesting good discriminative ability, and good fit (Hosmer–Lemeshow X^2 13.00, $df = 8$, $p = 0.112$). Propensity score adjusted variables were no longer significantly different between cohorts exposed to ≤24 or >24 h of corticosteroids (Table 4). Probability for receiving corticosteroid therapy >24 h varied linearly across quintiles of propensity score, and showed good matching between the cohorts exposed to ≤24 or >24 h of corticosteroids (Fig. 1). The propensity score quintile was introduced into the above regression models (Supplementary Tables 1–3) as a covariate. The propensity

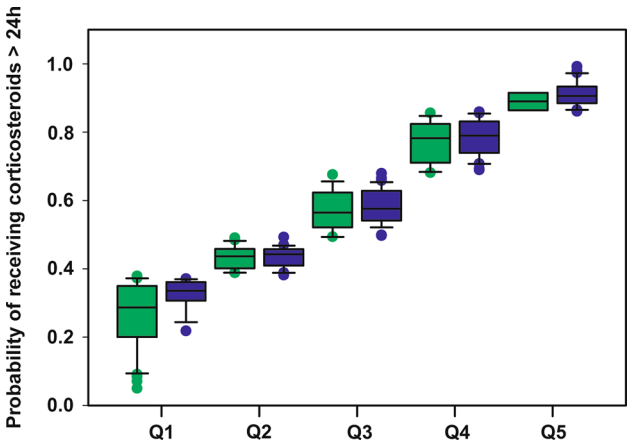

Fig. 1 Quintiles (Q) of propensity score between children exposed to either no or ≤24 h (*green*) or >24 h (*blue*) of corticosteroids

Table 5 Summary table of corticosteroid associations

	Mortality OR (95 % CI)	VFD coefficient (95 % CI)	(Log) duration of ventilation in survivors coefficient (95 % CI)
Corticosteroids >24 h			
Unadjusted	2.32 (1.05–5.12)	−3.40 (−5.50 to −1.31)	0.26 (0.05–0.46)
p	0.038	0.002	0.013
Covariate adjusted	1.85 (0.70–4.92)	−2.98 (−5.09 to −0.88)	0.30 (0.09–0.51)
p	0.218	0.006	0.005
Propensity adjusted	1.44 (0.51–4.09)	−2.88 (−5.05 to −0.71)	0.28 (0.06–0.50)
p	0.493	0.009	0.011
Cumulative dose of corticosteroids (mg/kg MPE)			
Unadjusted	1.02 (1.00–1.03)	−0.12 (−0.17 to −0.07)	0.02 (0.01–0.02)
p	0.025	<0.001	<0.001
Covariate adjusted	1.02 (1.00–1.04)	−0.13 (−0.18 to −0.07)	0.02 (0.01–0.03)
p	0.056	<0.001	<0.001
Propensity adjusted	1.02 (1.00–1.04)	−0.12 (−0.18 to −0.07)	0.02 (0.01–0.03)
p	0.101	<0.001	<0.001

adjusted models confirmed that corticosteroid exposure >24 h and cumulative corticosteroid dose were both independently associated with VFD and duration of mechanical ventilation in survivors, but not mortality. The results from different models are summarized in Table 5.

Subgroup analysis

To test associations in more homogenous subgroups, we assessed the association between corticosteroid exposure >24 h and outcome in immunocompetent children, in patients with PARDS resulting from a pulmonary or non-pulmonary infection requiring vasopressor support (and therefore meeting criteria for septic shock [24]), and in children with reactive airway disease or lung disease of prematurity (Supplementary Table 4). In no subgroup was benefit seen with corticosteroids. In immunocompetent children, corticosteroid exposure >24 h was associated with longer duration of ventilation in survivors and fewer VFD.

High-risk subgroups

We performed additional analyses assessing the association between corticosteroid exposure >24 h and outcomes in three prospectively defined high-risk cohorts: patients with ≥3 non-pulmonary organ failures ($n = 76$, 34 % mortality), immunocompromised patients ($n = 54$, 35 % mortality), and patients with severe PARDS (worst OI ≥16 [17], $n = 101$, 22 % mortality). There was no evidence of benefit with corticosteroids in any subgroup. In patients with ≥3 non-pulmonary organ failures and immunocompromised conditions, corticosteroid exposure >24 h was associated with fewer VFD (Supplementary Table 5).

PICU-acquired infections

In univariate analysis, both corticosteroid exposure >24 h and cumulative corticosteroid dose were associated with more PICU-acquired infections (Table 1). This association was not significant after adjustment for duration of mechanical ventilation for either corticosteroid exposure >24 h ($p = 0.221$) or cumulative corticosteroid dose ($p = 0.134$).

Discussion

In this PARDS cohort, exposure to corticosteroids >24 h was associated with fewer VFD and longer duration of ventilation in survivors. These results persisted after covariate and propensity adjustment. Corticosteroid use >24 h was prevalent (60 %), with hydrocortisone accounting for over half of the initial prescription, and resulted in substantial cumulative dosage during ventilation. Despite not being utilized solely for refractory hypoxemia or for persistent PARDS, children nevertheless experienced substantial corticosteroid exposure. Given the association with prolonged mechanical ventilation, this study has relevance for clinical practice.

The cohort exposed to corticosteroid >24 h showed greater severity of illness (Table 1). Corticosteroid use, either for hemodynamic ("stress dosing") or for pulmonary indications, was not protocolized and was left to the discretion of the prescribing physician. To address this potential source of bias, in addition to propensity and covariate adjustment, we examined the association between corticosteroid exposure >24 h and outcomes in prospectively defined subgroups, including several high-risk subgroups. No subgroup showed benefit with corticosteroid exposure (Supplementary Tables 4 and 5).

A single report of PARDS documented the unadjusted association between corticosteroid exposure and increased mortality [7]. We find a similar unadjusted association in this study, but do not find an independent association between corticosteroid exposure >24 h and mortality after adjustment for severity of illness. We do find fewer VFD and increased duration of ventilation in survivors after multivariate and propensity adjustments. A recent pilot, placebo-controlled randomized trial investigating low-dose methylprednisolone (2 mg/kg bolus and 1 mg/kg/day on days 1–7, weaned on days 8–14) for PARDS demonstrated feasibility, but no effect on mortality, VFD, or duration of ventilation [4]. Importantly, immunocompromised patients and patients with prior corticosteroid exposure were excluded from this trial, making comparison with our cohort difficult. The dose used in this feasibility trial was consistent with the range observed in our cohort, although the duration was longer in the trial (14 days).

Our conclusions are consistent with the reported associations of worse outcomes and corticosteroids in pediatric sepsis [21, 28] and congenital heart surgery [29]. Potential mechanisms for the worse outcomes include neuromuscular weakness exacerbated by corticosteroids, rebound inflammation upon discontinuation of corticosteroids, and immunosuppression. While PICU-acquired infections were associated with corticosteroid exposure >24 h in unadjusted analysis, the association was not confirmed after adjustment for duration of ventilation.

The methylprednisolone dose used in adult ARDS trials ranges from 1 to 2 mg/kg/day [1–3], within the range we observed. One finding of this study was the significant contribution of hydrocortisone towards cumulative corticosteroid exposure, a factor not typically adjusted for in methylprednisolone trials. While the percentage of patients (60 %) exposed to corticosteroids >24 h seems high for PARDS, this likely reflected the inclusion of all corticosteroid exposure, including hydrocortisone, which was likely used for refractory shock. Future trials should account for the contribution of additional corticosteroids towards outcomes and adverse effects, as complete exclusion of patients receiving hydrocortisone may further limit patient recruitment and generalizability of results.

Timing, duration, and intensity of steroid exposure may all be important aspects of corticosteroid exposure. Timing of corticosteroids, in particular, remains controversial. ARDSNet [2] demonstrated higher mortality for patients started on methylprednisolone 14 days after onset of ARDS, whereas observational studies [5, 6] associated early (<3 days) treatment with worse outcomes in adults with H1N1-ARDS. In the cohort exposed to corticosteroids >24 h, patients received corticosteroids at a median 0 days after meeting PARDS criteria, with 89 % receiving them within 3 days, thereby precluding assessment of the effect of timing of corticosteroid exposure on outcome. Additionally, duration of corticosteroid exposure in this cohort (median 7 [IQR 5, 12] days) is less than recommended by some experts [1, 3], with concerns cited for rebound inflammation after discontinuation [2, 30]. This is further confounded by the lack of standardization of corticosteroid initiation, weaning, and termination in this study. Recommendations for timing, intensity, and duration of corticosteroids in critically ill children, for either refractory shock or PARDS, remain uncertain, necessitating an adequately powered, prospective interventional study.

This study has several strengths. It was prospectively conducted in a large PICU in children meeting all three contemporary definitions of ARDS. Detailed demographic, ventilator, laboratory, and medication data were collected. Multiple analytic approaches were applied to minimize confounding. However, our study has important limitations. Outcomes reported are short term, and we were unable to collect information on neuromyopathy or functional outcome status. The study was conducted at a single center, and while demographics and severity of illness are comparable to other PARDS cohorts, mortality rate, ventilator practices, utilization of ancillary therapies, and fluid and sedation management were not protocolized, and may not allow generalizability to other PICUs. Finally, the observational nature of the study precludes the ability to make conclusions regarding causality between corticosteroid exposure >24 h and outcomes, and the possibility of confounding by indication remains. Rather, we are limited to identifying important associations for future hypothesis generation and testing.

Conclusion

In this cohort of PARDS, corticosteroid exposure >24 h and cumulative corticosteroid dose were associated with fewer VFD and longer duration of invasive mechanical ventilation in survivors. Results persisted after adjustment for confounders, including severity of illness, oxygenation index, immunocompromised status, and number of organ failures. In multiple subgroup analyses, no benefit was seen for corticosteroids.

Acknowledgments We would like to thank Xuemei Zhang and our colleagues at Westat Biostatistics and Data Management Core for statistical support and analysis. We thank the CHOP Virtual PICU Systems team for assistance with PRISM III scoring.

Conflicts of interest Dr. Neal J. Thomas reports personal fees from Discovery Labs, personal fees from Ikaria, and grants from the US Food and Drug Administration, all outside of the submitted work. The remaining authors declare no conflicts of interest.

References

1. Meduri GU, Headley AS, Golden E, Carson SJ, Umberger RA, Kelso T, Tolley EA (1998) Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: a randomized controlled trial. JAMA 280:159–165
2. Steinberg KP, Hudson LD, Goodman RB, Hough CL, Lanken PN, Hyzy R, Thompson BT, Ancukiewicz M (2006) Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. N Engl J Med 354:1671–1684
3. Meduri GU, Golden E, Freire AX, Taylor E, Zaman M, Carson SJ, Gibson M, Umberger R (2007) Methylprednisolone infusion in early severe ARDS: results of a randomized controlled trial. Chest 131:954–963
4. Drago BB, Kimura D, Rovnaghi CR, Schwingshackl A, Rayburn M, Meduri GU, Anand KJ (2015) Double-blind, placebo-controlled pilot randomized trial of methylprednisolone infusion in pediatric acute respiratory distress syndrome. Pediatr Crit Care Med 16:e74–e81
5. Kim SH, Hong SB, Yun SC, Choi WI, Ahn JJ, Lee YJ, Lee HB, Lim CM, Koh Y, Korean Society of Critical Care Medicine HNC (2011) Corticosteroid treatment in critically ill patients with pandemic influenza A/H1N1 2009 infection: analytic strategy using propensity scores. Am J Respir Crit Care Med 183:1207–1214
6. Brun-Buisson C, Richard JC, Mercat A, Thiebaut AC, Brochard L, Group R-SAHNvR (2011) Early corticosteroids in severe influenza A/H1N1 pneumonia and acute respiratory distress syndrome. Am J Respir Crit Care Med 183:1200–1206
7. Wong JJ, Loh TF, Testoni D, Yeo JG, Mok YH, Lee JH (2014) Epidemiology of pediatric acute respiratory distress syndrome in Singapore: risk factors and predictive respiratory indices for mortality. Front Pediatr 2:78
8. Peter JV, John P, Graham PL, Moran JL, George IA, Bersten A (2008) Corticosteroids in the prevention and treatment of acute respiratory distress syndrome (ARDS) in adults: meta-analysis. BMJ 336:1006–1009
9. Wong HR, Cvijanovich NZ, Allen GL, Thomas NJ, Freishtat RJ, Anas N, Meyer K, Checchia PA, Weiss SL, Shanley TP, Bigham MT, Banschbach S, Beckman E, Harmon K, Zimmerman JJ (2014) Corticosteroids are associated with repression of adaptive immunity gene programs in pediatric septic shock. Am J Respir Crit Care Med 189:940–946
10. Trachsel D, McCrindle BW, Nakagawa S, Bohn D (2005) Oxygenation index predicts outcome in children with acute hypoxemic respiratory failure. Am J Respir Crit Care Med 172:206–211
11. Flori HR, Glidden DV, Rutherford GW, Matthay MA (2005) Pediatric acute lung injury: prospective evaluation of risk factors associated with mortality. Am J Respir Crit Care Med 171:995–1001
12. Erickson S, Schibler A, Numa A, Nuthall G, Yung M, Pascoe E, Wilkins B, Paediatric Study Group, Australian, New Zealand Intensive Care Society (2007) Acute lung injury in pediatric intensive care in Australia and New Zealand: a prospective, multicenter, observational study. Pediatr Crit Care Med 8:317–323
13. Khemani RG, Markovitz BP, Curley MA (2009) Characteristics of children intubated and mechanically ventilated in 16 PICUs. Chest 136:765–771
14. Lopez-Fernandez Y, Azagra AM, de la Oliva P, Modesto V, Sanchez JI, Parrilla J, Arroyo MJ, Reyes SB, Pons-Odena M, Lopez-Herce J, Fernandez RL, Kacmarek RM, Villar J, Pediatric Acute Lung Injury Epidemiology and Natural History (PED-ALIEN) Network (2012) Pediatric Acute Lung Injury Epidemiology and Natural History study: incidence and outcome of the acute respiratory distress syndrome in children. Crit Care Med 40:3238–3245
15. De Luca D, Piastra M, Chidini G, Tissieres P, Calderini E, Essouri S, Medina Villanueva A, Vivanco Allende A, Pons-Odena M, Perez-Baena L, Hermon M, Tridente A, Conti G, Antonelli M, Kneyber M, Respiratory Section of the European Society for Pediatric Neonatal Intensive Care (2013) The use of the Berlin definition for acute respiratory distress syndrome during infancy and early childhood: multicenter evaluation and expert consensus. Intensive Care Med 39:2083–2091
16. Yehya N, Servaes S, Thomas NJ (2015) Characterizing degree of lung injury in pediatric acute respiratory distress syndrome. Crit Care Med 43:937–946
17. Pediatric Acute Lung Injury Consensus Conference Group (2015) Pediatric acute respiratory distress syndrome: consensus recommendations from the pediatric acute lung injury consensus conference. Pediatr Crit Care Med 16:428–439
18. Santschi M, Jouvet P, Leclerc F, Gauvin F, Newth CJ, Carroll CL, Flori H, Tasker RC, Rimensberger PC, Randolph AG, PALIVE Investigators, Pediatric Acute Lung Injury and Sepsis Investigators Network (PALISI), European Society of Pediatric and Neonatal Intensive Care (ESPNIC) (2010) Acute lung injury in children: therapeutic practice and feasibility of international clinical trials. Pediatr Crit Care Med 11:681–689
19. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS (2012) Acute respiratory distress syndrome: the Berlin definition. JAMA 307:2526–2533
20. Mager DE, Lin SX, Blum RA, Lates CD, Jusko WJ (2003) Dose equivalency evaluation of major corticosteroids: pharmacokinetics and cell trafficking and cortisol dynamics. J Clin Pharmacol 43:1216–1227
21. Markovitz BP, Goodman DM, Watson RS, Bertoch D, Zimmerman J (2005) A retrospective cohort study of prognostic factors associated with outcome in pediatric severe sepsis: what is the role of steroids? Pediatr Crit Care Med 6:270–274
22. Atkinson SJ, Cvijanovich NZ, Thomas NJ, Allen GL, Anas N, Bigham MT, Hall M, Freishtat RJ, Sen A, Meyer K, Checchia PA, Shanley TP, Nowak J, Quasney M, Weiss SL, Banschbach S, Beckman E, Howard K, Frank E, Harmon K, Lahni P, Lindsell CJ, Wong HR (2014) Corticosteroids and pediatric septic shock outcomes: a risk stratified analysis. PLoS One 9:e112702
23. Wernovsky G, Wypij D, Jonas RA, Mayer JE Jr, Hanley FL, Hickey PR, Walsh AZ, Chang AC, Castaneda AR, Newburger JW, Wessel DL (1995) Postoperative course and hemodynamic profile after the arterial switch operation in neonates and infants. A comparison of low-flow cardiopulmonary bypass and circulatory arrest. Circulation 92:2226–2235
24. Goldstein B, Giroir B, Randolph A, International Consensus Conference on Pediatric Sepsis (2005) International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med 6:2–8

25. Yehya N, Topjian AA, Lin R, Berg RA, Thomas NJ, Friess SH (2014) High frequency oscillation and airway pressure release ventilation in pediatric respiratory failure. Pediatr Pulmonol 49:707–715
26. Yehya N, Topjian AA, Thomas NJ, Friess SH (2014) Improved oxygenation 24 hours after transition to airway pressure release ventilation or high-frequency oscillatory ventilation accurately discriminates survival in immunocompromised pediatric patients with acute respiratory distress syndrome. Pediatr Crit Care Med 15:e147–e156
27. Horan TC, Andrus M, Dudeck MA (2008) 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 36:309–332
28. Wong HR, Cvijanovich NZ, Anas N, Allen GL, Thomas NJ, Bigham MT, Weiss SL, Fitzgerald J, Checchia PA, Meyer K, Shanley TP, Quasney M, Hall M, Gedeit R, Freishtat RJ, Nowak J, Shekhar RS, Gertz S, Dawson E, Howard K, Harmon K, Beckman E, Frank E, Lindsell CJ (2015) Developing a clinically feasible personalized medicine approach to pediatric septic shock. Am J Respir Crit Care Med 191:309–315
29. Pasquali SK, Hall M, Li JS, Peterson ED, Jaggers J, Lodge AJ, Marino BS, Goodman DM, Shah SS (2010) Corticosteroids and outcome in children undergoing congenital heart surgery: analysis of the pediatric health information systems database. Circulation 122:2123–2130
30. Annane D (2007) Glucocorticoids for ARDS: just do it! Chest 131:945–946