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CORTISOL CORRELATES WITH SEVERITY OF ILLNESS AND POORLY REFLECTS ADRENAL FUNCTION IN PEDIATRIC ACUTE RESPIRATORY DISTRESS SYNDROME

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Abstract

Objective—To test the association between random cortisol and severity of illness in a “real-world” application of current guidelines.

Study design—We performed a secondary analysis of a prospective observational cohort of acute respiratory distress syndrome (ARDS). Children with ARDS and vasopressor-dependent shock were identified and random cortisol levels prior to potential hydrocortisone initiation recorded. The cohort was dichotomized to cortisol < 18 µg/dL and ≥ 18 µg/dL, and hydrocortisone use and outcomes compared.

Results—Of 357 children with ARDS, 155 (15 non-survivors, 10%) had vasopressors initiated with cortisol drawn prior to possible hydrocortisone use. Patients with cortisol < 18 µg/dL had lower severity of illness scores, fewer organ failures, and lower vasopressor scores (all rank-sum $p < 0.05$). No benefit was seen with hydrocortisone in either the entire cohort, or when dichotomized by a cortisol cutoff of 18 µg/dL. In patients with cortisol ≥ 18 µg/dL, hydrocortisone was associated with increased mortality after adjustment for either organ dysfunction or vasopressor score.

Conclusions—In children with ARDS with vasopressor-dependent shock, low cortisol correlated with lower severity of illness. Random cortisol was a poor method of diagnosing

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adrenal insufficiency, and a strategy of hydrocortisone replacement for cortisol < 18 µg/dL did not target a population likely to benefit from hydrocortisone. Future guidelines should reconsider using random cortisol levels alone for assessing adrenal function.

Keywords

acute respiratory distress syndrome; ARDS; pediatric acute respiratory distress syndrome; cortisol; shock

The role of corticosteroid therapy in critically ill children with shock is controversial. It is unclear how best to identify the patients in whom hydrocortisone may be beneficial. This uncertainty is reflected in the ambiguity of the 2008 (1) and 2012 (2) Surviving Sepsis Guidelines, which suggest that random cortisol levels can identify adrenal insufficiency. The 2008 guidelines state that for adults “adrenal insufficiency in the case of catecholamine-resistant septic shock is assumed at a random total cortisol concentration < 18 µg/dL.” The 2012 adult guidelines confirm that an “inappropriately low random cortisol level (< 18 µg/dL) in a patient with shock would be considered an indication for steroid therapy.” Others have also advocated random cortisol measurements to identify adrenal insufficiency (3). Furthermore, performing adrenocorticotropic (ACTH) stimulation tests is not recommended (1, 2), as the two largest trials of corticosteroids in sepsis failed to demonstrate an interaction between hydrocortisone replacement and response to ACTH on mortality (4, 5). Additionally, ACTH stimulation is cumbersome in acute situations, rendering it impractical for assessing which patients should receive hydrocortisone.

The rationale for identifying patients with adrenal failure manifest by low cortisol levels (often called “absolute adrenal insufficiency”) is predicated on prompt recognition of Addisonian crisis (6-8), with specific references to cortisol < 18 µg/dL portending increased mortality in meningococemia (6, 7). However, other investigators have associated lower cortisol levels with lower severity of illness and lower mortality risk (9-11). Several studies suggest “relative adrenal insufficiency,” defined by some investigators as an inadequate response to 250 µg ACTH simulation (increment 9 µg/dL), carries a stronger association with poor outcome (12-14). From a practical standpoint, 61.4% of pediatric intensivists use only random cortisol as their sole criterion for initiating or continuing hydrocortisone (15).

Although most studies of hydrocortisone are in septic shock, critical illness-related corticosteroid insufficiency may exist in other inflammatory conditions. Observational studies and clinical trials demonstrate use of hydrocortisone in polytrauma (16), traumatic brain injury (17), congenital heart disease surgery (18, 19), and acute respiratory distress syndrome (ARDS) (20, 21). Appropriate recommendations regarding which patients would benefit from hydrocortisone is critical to ensure that the benefits of treatment are not outweighed by the risks of corticosteroids. Application of current Surviving Sepsis recommendations may expose patients without adrenal insufficiency, but with low cortisol levels (< 18 µg/dL), to unnecessary hydrocortisone.

Since July, 2011, the Children's Hospital of Philadelphia (CHOP) has maintained a prospective database of pediatric ARDS. This cohort experienced substantial corticosteroid exposure (22), including hydrocortisone for refractory shock, extrapolating from the

Surviving Sepsis recommendations. To test the association between random total cortisol levels and severity of illness in a “real-world” application of current guidelines, we conducted a secondary analysis of this cohort.

METHODS

This study is a secondary analysis of a prospectively collected ARDS cohort. The study was approved by CHOP's Institutional Review Board, and requirement for informed consent waived. Consecutive patients in the pediatric intensive care unit (PICU) were screened daily for eligibility between July 1, 2011 and June 30, 2015. The inclusion and exclusion criteria have been described before (22, 23). Briefly, children (between 1 month and 18 years) undergoing invasive mechanical ventilation meeting American-European Consensus Conference (AECC)(24) criteria for acute lung injury (ALI, $P_{aO_2}/F_{iO_2} \leq 300$ on 2 consecutive arterial blood gases separated by ≥ 1 hour and bilateral parenchymal infiltrates) were eligible. As the study was initiated prior to 2012 Berlin ARDS definition (25), we did not specify a minimum positive end-expiratory pressure (PEEP); however, we do not utilize $PEEP < 5$ cmH₂O; therefore, all patients met Berlin criteria. Similarly, as these data were collected prior to the 2015 Pediatric Acute Lung Injury Consensus Conference (PALICC) definitions of pediatric ARDS (26), children who met ARDS criteria by non-invasive (SpO_2) criteria were not enrolled; however, all children met ARDS criteria by invasive (oxygenation index, OI) criteria.

To identify children with fluid-refractory shock within this cohort, we restricted analysis to patients on vasopressor infusions and available cortisol levels drawn prior to potential treatment with hydrocortisone. We excluded patients with shock and purpura, prior corticosteroid use within the past month, and known central or primary adrenal insufficiency as evidenced by a listed diagnosis in the medical record or home hydrocortisone use. Patients were followed for whether hydrocortisone was continued or discontinued beyond the initial dose, typically when the random cortisol level resulted.

Corticosteroids in Shock Management

Corticosteroid use was identified as a variable of interest, and detailed information on corticosteroid use, type, dosage, and duration was collected. Actual doses were verified by reconciliation with nursing medication administration record. CHOP employs a protocolized approach to septic shock patterned after the Surviving Sepsis guidelines. Specific recommendations are made for hydrocortisone in catecholamine refractory shock, defined as persistent hypotension after titration of a single vasopressor and adequate fluid resuscitation, with an initial bolus of 100 mg/m² followed by 100 mg/m²/day divided every 4 hours. The protocol recommends discontinuing hydrocortisone if the random cortisol level drawn prior to the initial bolus dose is ≥ 18 µg/dL.

Other Equations and Definitions

Metrics of oxygenation were P_{aO_2}/F_{iO_2} and OI ($(\text{mean airway pressure [mPaw]} \times F_{iO_2} \times 100)/P_{aO_2}$). The vasopressor score (27-29) was calculated by: dopamine (µg/kg/min) $\times 1$ + dobutamine (µg/kg/min) $\times 1$ + epinephrine (µg/kg/min) $\times 100$ + norepinephrine (µg/kg/min)

$\times 100 + \text{phenylephrine } (\mu\text{g/kg/min}) \times 100 + \text{vasopressin } (\text{U/kg/min}) \times 10,000 + \text{milrinone } (\mu\text{g/kg/min}) \times 10$. Non-pulmonary organ failures at time of ARDS diagnosis were identified using accepted definitions in children (30). The designation of “immunocompromised” (23, 31) required presence of an immunocompromising diagnosis (oncologic, immunologic, rheumatologic, or transplant) and active immunosuppressive chemotherapy, or congenital immunodeficiency. Severity of illness score used was the Pediatric Risk of Mortality (PRISM) III using data from the first 12 hours of PICU admission.

The primary reported outcome was mortality. Ventilator-free days (VFD) at 28 days and duration of mechanical ventilation were also recorded. All mention of “mechanical ventilation” in this study implies invasive ventilation, and non-invasive support was not counted. For VFD and duration of mechanical ventilation, the first day was initiation of invasive ventilation. Liberation from invasive ventilation for > 24 hours defined duration of mechanical ventilation. Patients requiring re-initiation of invasive ventilation after 24 hours 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.

Statistical Analyses

Data are expressed as percentages or as median [interquartile range, IQR]. All variables were found to be non-normally distributed by Shapiro–Wilk. Differences between distributions of categorical variables were analyzed by Fisher's exact test. Continuous variables were compared using Wilcoxon rank sum or signed-rank as appropriate. To test the association between hydrocortisone exposure and mortality, a two-variable logistic regression model was constructed, with hydrocortisone exposure retained in every model alongside (separately) PRISM III, non-pulmonary organ dysfunctions, and vasopressor score (log-transformed). Models were assessed for goodness of fit with Hosmer-Lemeshow statistics. Some variables were log-transformed to achieve a normal distribution for correlation and regression analyses. Data were analyzed using Stata 10.0 (StataCorp, LP, College Station, TX).

RESULTS

Of the total cohort of 357 children with ARDS, 155 had vasopressor-dependent shock with an available cortisol level drawn before hydrocortisone administration. Of these 155 children, hydrocortisone was continued in 84 (54%; Table I). An additional 29 patients had an initial bolus of hydrocortisone, with discontinuation after cortisol levels were available. Patients with cortisol $< 18 \mu\text{g/dL}$ (Table I) were less sick, with lower PRISM III, fewer organ dysfunctions, and lower vasopressor scores (all $p < 0.01$). Despite lower vasopressor scores, patients with cortisol $< 18 \mu\text{g/dL}$ were more likely to have hydrocortisone continued (68% continued for cortisol $< 18 \mu\text{g/dL}$ versus 44% for $\geq 18 \mu\text{g/dL}$, $p = 0.004$). Results were similar when the cohort was dichotomized by cortisol < 10 or $\geq 10 \mu\text{g/dL}$ or by restricting analysis to children with an infectious etiology (Tables II and III; available at www.jpeds.com). Random cortisol levels were modestly correlated with severity of illness ($p = 0.001$) and vasopressor score ($p = 0.002$; Figure).

Vasopressor scores significantly dropped over 24 hours both in patients in whom hydrocortisone was discontinued (from 12 [IQR 5, 20] to 7 [IQR 0, 12], signed-rank $p < 0.001$), as well as those in whom it was continued (from 15 [IQR 10, 29] to 7 [IQR 2, 14.5], signed-rank $p < 0.001$). At 24 hours after initial cortisol measurement, vasopressor scores were similar in both patients receiving and not receiving hydrocortisone (Table IV).

In children with random cortisol $< 18 \mu\text{g/dL}$, hydrocortisone was continued in 44 of 65 (68%), without differences in VFD at 28 days or mortality (Table IV). In patients with cortisol $\geq 18 \mu\text{g/dL}$, hydrocortisone was continued in 40 of 90 (44%) children. Patients with cortisol $\geq 18 \mu\text{g/dL}$ treated with hydrocortisone had higher PRISM III ($p = 0.006$) and higher vasopressor scores ($p < 0.001$). There was no evidence of benefit with hydrocortisone treatment in children with cortisol $\geq 18 \mu\text{g/dL}$, with fewer VFD ($p = 0.007$) and higher mortality ($p = 0.010$) in the hydrocortisone group (Table x). In bivariate analysis, in patients with cortisol $\geq 18 \mu\text{g/dL}$, hydrocortisone treatment was associated with increased mortality after adjustment for either organ dysfunction or initial vasopressor score (Table V).

DISCUSSION

In this cohort of children with ARDS, patients with cortisol $< 18 \mu\text{g/dL}$ had lower PRISM III, less organ dysfunction, and lower vasopressor scores. Random cortisol levels were correlated with severity of illness. Results were similar when the cohort was dichotomized by cortisol < 10 or $\geq 10 \mu\text{g/dL}$, or by ARDS with an infectious etiology. No benefit was seen with hydrocortisone in either the entire cohort or when dichotomized by cortisol < 10 or $\geq 10 \mu\text{g/dL}$, and in patients with cortisol $\geq 18 \mu\text{g/dL}$, hydrocortisone was independently associated with mortality. A cortisol cutoff of $< 18 \mu\text{g/dL}$ did not identify patients at risk for increased mortality.

The 2012 Surviving Sepsis Guidelines suggest not using an ACTH stimulation test to identify adults who may benefit from hydrocortisone, but suggest that an “inappropriately low random cortisol level ($< 18 \mu\text{g/dL}$) in a patient with shock would be considered an indication for steroid therapy” (grade 2B, weak recommendation with moderate quality evidence). The pediatric considerations suggest hydrocortisone therapy in children with “suspected or proven absolute adrenal insufficiency.” Similar to the adult recommendations, the pediatric guidelines suggest that “obtaining a serum cortisol at the time empiric hydrocortisone is administered may be helpful” (grade 1A, strong recommendation with high quality evidence). Both adult and pediatric guidelines imply that random cortisol levels are useful for identifying adrenal insufficiency, or in identifying a subgroup in whom hydrocortisone therapy may reasonably be expected to benefit. Our data do not support this. Unlike cohorts in which adrenal insufficiency is characterized by higher catecholamine use, more organ failure, and increased mortality (14, 32-34), “adrenal insufficiency” defined by cortisol $< 18 \mu\text{g/dL}$ in our cohort demonstrated lower PRISM III, less organ dysfunction, and lower vasopressor scores. These findings held when using the more conservative cutoff of $< 10 \mu\text{g/dL}$, as well.

Rapid identification of “absolute adrenal insufficiency” is predicated on prompt recognition of Addisonian crisis in patients with sepsis (2). These concerns are partly based on the

association between lower cortisol and increased mortality in pediatric meningococemia (6, 7). Interestingly, in both studies, non-survivors also had substantially higher ACTH levels, which may offer insight into adrenal function and its relationship with mortality. In both studies, regardless of whether cortisol was < 18 or $18 \mu\text{g/dL}$, all non-survivors demonstrated elevated ACTH concentrations, suggesting persistent pituitary stimulation with inadequate cortisol response. These results support the need for further hormonal testing, in addition to random cortisol measurements, to properly assess adrenal function during critical illness. In a general septic population not restricted to meningococemia, an adequate response to ACTH stimulation (14, 32-34) was more consistently associated with clinical signs of adrenal insufficiency, such as higher catecholamine use and increased mortality. A cutoff of random cortisol $< 18 \mu\text{g/dL}$ to identify adrenal insufficiency is also problematic because several sepsis cohort studies suggest that cortisol levels directly correlate with increased mortality, and are higher in non-survivors (14, 33, 35).

The differences between our results and other studies may reflect differences in study population. Fulminant meningococcal disease is known to cause a primary adrenal insult (36). However, the adaptive changes to the hypothalamic-pituitary-adrenal (HPA) axis in other critical illnesses, including all-cause septic shock and pediatric ARDS, may be quite different. An ACTH-cortisol “disassociation” has been described in critical illness (37). In such cases, increased cortisol reflected impaired cortisol clearance rather than increased ACTH release (38). These changes to the HPA axis may explain the correlation between elevated random cortisol levels and disease severity observed in this and other pediatric (14, 33) and adult (35) cohorts.

In addition to hormonal testing, clinical response to corticosteroid administration may give insight into adrenal function during critical illness, as patients with adrenal insufficiency would be expected to improve with glucocorticoid therapy. As in other pediatric cohorts (39-44), we saw no benefit with hydrocortisone use in patients, regardless of whether cortisol levels were < 18 or $18 \mu\text{g/dL}$. Although the lack of efficacy of hydrocortisone in observational studies is confounded by indication bias and greater shock severity in those treated with hydrocortisone, part of this may also be due to application of hydrocortisone in an inappropriate population. The enthusiasm for hydrocortisone was reignited after Annane et al (4) randomized adults with vasopressor-refractory septic shock within 8 hours to hydrocortisone + fludrocortisone versus placebo, demonstrating that steroid replacement hastened shock reversal and improved mortality, particularly in patients with inadequate cortisol response ($< 9 \mu\text{g/dL}$) to $250 \mu\text{g}$ ACTH. The subsequent negative CORTICUS trial (5), which allowed enrollment of patients in whom shock had resolved up to 72 hours, tempered enthusiasm by failing to reproduce these results, and cast further uncertainty about the utility of ACTH stimulation. The lower mortality in CORTICUS highlights the importance of patient selection and illness severity in determining which population may benefit from hydrocortisone. The 2012 Surviving Sepsis Guidelines emphasize that in patients with low mortality risk, there appears to be no mortality benefit with hydrocortisone replacement, but that there may be possible benefit in patients with higher baseline risk (2). In this cohort of children with ARDS, we demonstrate that random cortisol $< 18 \mu\text{g/dL}$ does not identify a high risk subgroup likely to benefit from hydrocortisone replacement.

The results of this and similar studies pose the question as to the most appropriate test to assess adrenal function in critical illness. Despite the fact that positive results in the study by Annane et al seemed driven by “non-responders” to ACTH stimulation (increment 9 µg/dL), the interaction between corticosteroid use and response to ACTH was not significant (4). Similarly, there was no distinction between responders and non-responders in CORTICUS (5). These results contributed to the recommendation against ACTH stimulation testing to identify a cohort at risk for adrenal insufficiency, a recommendation heeded by many pediatric practitioners (15), the majority of whom restrict their hydrocortisone decisions to a random cortisol level alone. In addition to the lack of clear evidence that ACTH stimulation is useful in the face of conflicting evidence, there are practical limitations to conducting ACTH stimulation in the acute setting. Based on the pediatric meningococemia literature (6, 7), a random cortisol:ACTH ratio may be an acceptable test of adrenal function, with lower ratios evidence of inappropriately elevated ACTH and inadequate cortisol production. ACTH assays require immediate placement on ice after collection, but may be an appealing alternative, as they only require collection at a single time-point. Whether we utilize ACTH stimulation, cortisol:ACTH ratios, or some other adrenal assessment, our study suggests that random cortisol alone is a poor method of diagnosing adrenal insufficiency in ARDS, and is unlikely to identify a population likely to benefit from hydrocortisone. Appropriate recommendations regarding which patients would benefit from hydrocortisone is critical to ensure that the benefits of treatment are not outweighed by the risks of corticosteroids, including immunosuppression, hospital acquired infections, hyperglycemia, neuromyopathy, and functional impairment.

This study has several strengths. Detailed demographic, laboratory, and medication data were collected prospectively. The size of the cohort is larger than comparable studies of adrenal function in critically ill children, and represents a “real world” application of current guidelines for hydrocortisone use. However, our study has important limitations. The cohort is not a population with septic shock, but ARDS with vasopressor-dependent shock. However, hydrocortisone is used for refractory shock in multiple populations without infection, including ARDS, traumatic brain injury, polytrauma, and low cardiac output after congenital heart disease surgery. Absent specific guidelines for these diagnoses, parameters for hydrocortisone use are often extrapolated from Surviving Sepsis. The study was conducted at a single center, and even though demographics and severity of illness are comparable with other cohorts of children with ARDS, the mortality rate and hydrocortisone protocol may not allow generalizability to other PICUs. However, similar to most pediatric intensivists (15), random cortisol is the sole determinant of hydrocortisone treatment in this study. The low mortality rate precluded the ability to fully explore the relationship between hydrocortisone use and mortality, as the number of variables included in multivariable models were limited. Finally, the observational nature of the study precludes the ability to make conclusions regarding the association between low cortisol levels and lower mortality, as well as the lack of utility of hydrocortisone. Rather, we are limited to identifying associations for future hypothesis generation and testing.

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ABBREVIATIONS

AECC	American European Consensus Conference
ACTH	adrenocorticotrophic hormone
ARDS	acute respiratory distress syndrome
CHOP	Children's Hospital of Philadelphia
OI	oxygenation index
PALICC	Pediatric Acute Lung Injury Consensus Conference
ARDS	Acute respiratory distress syndrome
PEEP	positive end-expiratory pressure
PICU	pediatric intensive care unit
PRISM III	Pediatric Risk of Mortality III
VFD	ventilator-free days

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Figure.

(A) Scatter plots showing correlation of PRISM III and log-transformed cortisol concentrations and (B) correlation of log-transformed vasopressor scores and log-transformed cortisol concentrations. Pearson correlation coefficients and associated p values are displayed.

Table 1

Characteristics of the cohort of children with ARDS with vasopressor-dependent shock.

	All patients (n =155)	Cortisol < 18 µg/dL (n = 65)	Cortisol ≥ 18 µg/dL (n = 90)	p value
Age (years)	5.3 [1.8, 12.8]	4.1 [1.7, 13.1]	5.6 [1.8, 11.9]	0.724
PRISM III at 12 hours	11 [6, 19]	8 [5, 2]	15 [9, 21]	< 0.001
Immunocompromised (%)	25 (16)	11 (17)	14 (16)	0.819
Cause of PARDS (%)				
Infectious pneumonia	81 (52)	41 (63)	40 (44)	0.096
Aspiration pneumonia	13 (8)	3 (4.5)	10 (11)	
Non-pulmonary sepsis	44 (28)	15 (23)	29 (32)	
Trauma	10 (6)	5 (8)	5 (6)	
Other	7 (5)	1 (1.5)	6 (7)	
Non-pulmonary organ dysfunctions at PARDS onset	2 [1, 3]	1 [1, 2]	2 [1, 3]	0.010
Vasopressor score				
At time of cortisol measurement	15 [7, 25]	11 [7, 17]	17.5 [8, 30]	0.009
24 hours after measurement	7 [2, 28]	6 [2, 10]	8 [0, 17]	0.021
Hydrocortisone continued (%)	84 (54)	44 (68)	40 (44)	0.004
First 24 hours of PARDS				
Worst PaO ₂ /FIO ₂	136 [95, 176]	131 [79, 165]	138 [100, 185]	0.447
Worst OI	11.6 [8.7, 19.4]	11.5 [8.7, 20.4]	11.6 [8.1, 19.1]	0.939
Outcomes				
VFD at 28 days	17 [7, 21]	15 [8, 19]	17.5 [6, 22]	0.142
PICU deaths (%)	15 (10)	4 (6)	11 (12)	0.207

Table II

Cohort dichotomized by Cortisol < 10 µg/dL or ≥ 10 µg/dL

	Cortisol < 10 µg/dL (n = 36)	Cortisol ≥ 10 µg/dL (n = 119)	p value
Age (years)	4.5 [1.8, 12.1]	5.3 [1.8, 12.9]	0.829
PRISM III at 12 hours	6 [3.5, 11]	12 [8, 20]	< 0.001
Immunocompromised (%)	3 (8)	22 (18)	0.147
Cause of PARDS (%)			
Infectious pneumonia	23 (64)	58 (49)	0.723
Aspiration pneumonia	2 (5.5)	11 (9)	
Non-pulmonary sepsis	8 (22)	36 (30)	
Trauma	2 (5.5)	8 (7)	
Other	1 (3)	6 (5)	
Non-pulmonary organ dysfunctions at PARDS onset	1 [1, 2]	2 [1, 3]	0.005
Vasopressor score			
At time of cortisol measurement	10 [5.5, 16.5]	15 [8, 28]	0.012
24 hours after measurement	4.5 [1, 8.5]	8 [3, 14]	0.018
Hydrocortisone continued (%)	29 (81)	55 (46)	< 0.001
First 24 hours of PARDS			
Worst PaO ₂ /FIO ₂	134 [87, 161]	136 [96, 182]	0.480
Worst OI	12.1 [8.6, 19.6]	11.6 [8.8, 19.4]	0.890
Outcomes			
VFD at 28 days	15.5 [10, 19.5]	17 [6, 21]	0.522
PICU deaths (%)	1 (3)	14 (12)	0.110

Table III

Cohort restricted to those with infectious etiology and vasopressor-dependent shock (ie, septic shock).

	All patients (n = 125)	Cortisol < 18 µg/dL (n = 56)	Cortisol ≥ 18 µg/dL (n = 69)	p value
Age (years)	4.7 [1.6, 12.1]	3 [1.6, 12.2]	5.3 [1.6, 12.1]	0.500
PRISM III at 12 hours	11 [6, 17]	7.5 [5, 12]	14 [9, 20]	< 0.001
Immunocompromised (%)	19 (15)	8 (14)	11 (16)	0.798
Cause of PARDS (%)				
Infectious pneumonia	81 (65)	41 (73)	40 (58)	0.076
Non-pulmonary sepsis	44 (35)	15 (27)	29 (42)	
Non-pulmonary organ dysfunctions at PARDS onset	2 [1, 3]	1 [1, 2]	2 [1, 3]	0.009
Vasopressor score				
At time of cortisol measurement	14 [7, 23]	11 [7, 16]	16 [8, 28.5]	0.032
24 hours after measurement	7 [3, 12]	6 [3, 9.5]	8 [0, 15]	0.081
Hydrocortisone continued (%)	70 (56)	36 (64)	34 (50)	0.093
First 24 hours of PARDS				
Worst PaO ₂ /FIO ₂	146 [101, 175]	134 [92, 165]	148 [105, 189]	0.174
Worst OI	11.3 [8.4, 16.8]	11.1 [8.6, 19.5]	11.3 [8, 15.6]	0.575
Outcomes				
VFD at 28 days	16 [7, 21]	15.5 [8.5, 19]	17 [3.5, 21]	0.362
PICU deaths (%)	13 (10)	3 (5)	10 (14)	0.096

Table 4

Hydrocortisone use in children with ARDS and vasopressor-dependent shock.

	No hydrocortisone	Hydrocortisone	<i>p</i> value
Whole cohort			
Number of patients	71	84	
PRISM III	10 [5, 17]	12 [7, 20]	0.059
Non-pulmonary organ dysfunctions	2 [1, 3]	2 [1, 3]	0.993
Vasopressor score			
At cortisol measurement	12 [5, 20]	15 [10, 29]	0.017
24 hours after	7 [0, 12]	7 [2, 14.5]	0.432
VFD at 28 days	18 [12, 22]	14 [2, 19]	0.004
PICU deaths (%)	3 (4%)	12 (14%)	0.054
Cortisol < 18 µg/dL			
Number of patients	21	44	
PRISM III	6 [5, 11]	9 [5.5, 14]	0.201
Non-pulmonary organ dysfunctions	2 [1, 2]	1 [1, 2]	0.916
Vasopressor score			
At cortisol measurement	11 [5, 16]	10 [7, 17]	0.715
24 hours after	6 [3, 10]	5.5 [0, 9.5]	0.429
VFD at 28 days	17 [9, 19]	15 [4.5, 19]	0.704
PICU deaths (%)	1 (5)	3 (7)	1
Cortisol ≥ 18 µg/dL			
Number of patients	50	40	
PRISM III	11.5 [7, 20]	16.5 [12, 24.5]	0.006
Non-pulmonary organ dysfunctions	2 [1, 3]	2.5 [1, 3]	0.310
Vasopressor score			
At cortisol measurement	13.5 [5, 23]	26 [15, 35]	< 0.001
24 hours after	7.5 [0, 13]	12.5 [4.5, 26.5]	0.036
VFD at 28 days	19.5 [13, 22]	12.5 [0, 19.5]	0.007
PICU deaths (%)	2 (4)	9 (23)	0.010

Table V

Association of hydrocortisone use and mortality in bivariate analysis

Model	Odds ratio	95% confidence interval	p value
Whole cohort			
Hydrocortisone (yes)	3.78	1.02 to 13.97	0.046
Hydrocortisone (yes) + PRISM III	2.58	0.66 to 10.15	0.175
Hydrocortisone (yes) + organ dysfunctions	3.90	0.98 to 15.58	0.054
Hydrocortisone (yes) + vasopressor score (log)	3.18	0.85 to 11.97	0.087
Cortisol < 18 µg/dL			
Hydrocortisone (yes)	1.46	0.14 to 14.97	0.748
Hydrocortisone (yes) + PRISM III	0.88	0.07 to 10.67	0.919
Hydrocortisone (yes) + organ dysfunctions	1.31	0.11 to 15.53	0.829
Hydrocortisone (yes) + vasopressor score (log)	1.37	0.13 to 14.12	0.794
Cortisol ≥ 18 µg/dL			
Hydrocortisone (yes)	6.97	1.41 to 34.42	0.017
Hydrocortisone (yes) + PRISM III	4.32	0.81 to 23.06	0.087
Hydrocortisone (yes) + organ dysfunctions	6.40	1.21 to 33.92	0.029
Hydrocortisone (yes) + vasopressor score (log)	6.15	1.14 to 33.21	0.035