Cortisol Correlates with Severity of Illness and Poorly Reflects Adrenal Function in Pediatric Acute Respiratory Distress Syndrome

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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 before potential hydrocortisone initiation recorded. The cohort was dichotomized to cortisol < 18 and ≥ 18 μg/dL, and hydrocortisone use and outcomes compared.

Results Of 357 children with ARDS, 155 (15 nonsurvivors; 10%) had vasopressors initiated with cortisol drawn before 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 $P < .05$). 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 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. *(J Pediatr 2016;177:212-8)*.

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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 hormone (ACTH) stimulation tests is not recommended,[1,2] because the 2 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 meningococcemia.[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 of ≤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

ACTH	Adrenocorticotropic hormone
ARDS	Acute respiratory distress syndrome
PICU	Pediatric intensive care unit
PRISM	Pediatric Risk of Mortality
VFD	Ventilator-free days

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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 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 Children's Hospital of Philadelphia'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 of age) undergoing invasive mechanical ventilation meeting American-European Consensus Conference[24] criteria for acute lung injury (Pa_{O_2}/F_{IO_2} ≤300 on 2 consecutive arterial blood gases separated by ≥1 hour and bilateral parenchymal infiltrates) were eligible. Because the study was initiated before 2012 Berlin ARDS definition,[25] we did not specify a minimum positive end-expiratory pressure; however, we do not use a positive end-expiratory pressure of <5 cm_{H_2O}; therefore, all patients met Berlin criteria. Similarly, as these data were collected before the 2015 Pediatric Acute Lung Injury Consensus Conference definitions of pediatric ARDS,[26] children who met ARDS criteria by noninvasive (Sp_{O_2}) criteria were not enrolled; however, all children met ARDS criteria by invasive (oxygenation index) criteria.

To identify children with fluid-refractory shock within this cohort, we restricted this analysis to patients on vasopressor infusions and available cortisol levels drawn before potential treatment with hydrocortisone. We excluded patients with shock and purpura, 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. The Children's Hospital of Philadelphia uses 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/m^2 followed by 100 mg/m^2 per day divided every 4 hours. The protocol recommends discontinuing hydrocortisone if the random cortisol level drawn before the initial bolus dose is ≥18 μg/dL.

Other Equations and Definitions

Metrics of oxygenation were Pa_{O_2}/F_{IO_2} and oxygenation index ([mean airway pressure × F_{IO_2} × 100]/Pa_{O_2}). The vasopressor score[27-29] was calculated by 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 + vasopressin (U/kg/min) × 10,000 + milrinone (μg/kg/min) × 10. Nonpulmonary organ failures at time of ARDS diagnosis were identified using accepted definitions in children.[30] The designation of "immunocompromised"[23,31] required the 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 noninvasive 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 toward total ventilator days. VFD was determined by subtracting total ventilator days from 28 in survivors. All patients with total ventilator days of ≥28 days, and all PICU nonsurvivors were assigned a VFD of 0.

Statistical Analyses

Data are expressed as percentages or as median (IQR). All variables were found to be non-normally distributed by Shapiro–Wilk. Differences between distributions of categorical variables were analyzed by Fisher 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 2-variable logistic regression model was constructed, with hydrocortisone exposure retained in every model alongside (separately) PRISM III, nonpulmonary organ dysfunctions, and vasopressor score (log-transformed). Models were assessed for goodness of fit with Hosmer-Lemeshow statistics. Some variables were