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EVIDENCE OF ENDOTYPES IN PEDIATRIC ACUTE HYPOXEMIC RESPIRATORY FAILURE CAUSED BY SEPSIS

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Abstract

Objective: Sub-classification based on clinical or biologic commonalities (endotypes) is one approach to reduce heterogeneity in acute hypoxemic respiratory failure (AHRF). In adults, biomarker-defined endotypes of respiratory failure have been described, with differential outcome profiles and response to therapy. To date, no studies have tested whether endotypes exist in pediatric AHRF, although mRNA expression-based endotypes have been described in pediatric sepsis. The aim of the present study was to test whether endotypes identified in pediatric sepsis are applicable to pediatric AHRF.

Design: Secondary analysis of a previously reported microarray-based study of pediatric sepsis.

Setting: Multiple pediatric intensive care units in the United States.

Patients: Sixty-seven children with AHRF caused by sepsis.

Measurements and Main Results: Of the larger septic shock cohort, 67 met eligibility for AHRF. Twenty-three subjects were assigned to Endotype A, and 44 to Endotype B. Subjects assigned to Endotype A had over 4-fold greater unadjusted 28-day mortality, and nearly 3-fold greater rates of complicated course. The association with mortality (OR 8.0, 95% CI 1.6 to 41.0) and complicated course (OR 4.2, 95% CI 1.2 to 14.9) persisted after adjustment for age, severity of illness, and PaO_2/FIO_2.

Conclusions: Applying a previously reported endotyping strategy in children with septic shock identified endotypes of pediatric AHRF secondary to sepsis, with differential risk for poor outcomes. To our knowledge, this is the first demonstration of endotypes in pediatric respiratory

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failure. Our results support an investigation into using transcriptomics to identify mRNA-based endotypes in a dedicated, well-defined AHRF cohort.

Keywords

acute hypoxemic respiratory failure; AHRF; ARDS; endotypes; mRNA; gene expression

INTRODUCTION

Acute hypoxemic respiratory failure (AHRF), including acute respiratory distress syndrome (ARDS), encompasses multiple diverse etiologies, with significant variability in clinical presentation. Patient heterogeneity contributes to the absence of targeted therapies for AHRF. Sub-classification based on clinical or biologic commonalities (endotypes) is one approach to reduce variability. Adult ARDS has been sub-classified by etiology (direct or indirect) (1–3) and by biomarker profiles (1, 4). This strategy has demonstrated utility, with differential responses to positive end-expiratory pressure (4) and fluid management (5) reported between endotypes. To date, no studies have tested whether endotypes exist in pediatric respiratory failure. Previously, we have demonstrated the existence of two endotypes, A and B, in pediatric septic shock using peripheral mRNA-expression (6–8). Endotype A was characterized by repression of genes associated with adaptive immunity and glucocorticoid receptor signaling, and was independently associated with poor outcome. The aim of the present study was to test whether endotypes identified in septic shock are applicable to AHRF in children.

METHODS

This is a re-analysis of a previously reported microarray-based study of pediatric sepsis (6, 8, 9). All array data have been deposited in the National Center for Biotechnology Information Gene Expression Omnibus (Accession number GSE66099). The protocol was approved by each institution's institutional review board. Children ≤ 10 years of age admitted to the pediatric intensive care unit (PICU) meeting 2005 criteria for septic shock were eligible (10). After consent, blood was obtained within 24 hours of PICU presentation. Clinical and laboratory data were collected daily while in the PICU. Organ failure was defined using Goldstein criteria and tracked for seven days after PICU admission (10). Mortality was tracked for 28 days. Mortality risk was measured using Pediatric Risk for Mortality (PRISM) III scores from day of PICU admission, and septic shock–related mortality risk was estimated using the Pediatric Sepsis Biomarker Risk Model (PERSEVERE) (11, 12). For this study, we identified subjects with AHRF by selecting for invasively ventilated subjects with $PaO_2/FIO_2 \leq 200$ in the first seven days after admission.

Total RNA was isolated from whole blood using the PaxGene Blood RNA System (PreAnalytiX, Qiagen/Becton Dickson, Valencia, CA). In our initial work (6, 9), array hybridization was performed using the Human Genome U133 Plus 2.0 GeneChip (Affymetrix, Santa Clara, CA). Endotypes were assigned using the expression patterns of the 100 endotype-defining genes (8). We extracted expression data and generated individual visual gene expression patterns for each study subject using the Gene Expression Dynamics

Inspector. These were compared to reference patterns using computer-assisted image analysis to assign the study subjects into either Endotype A or B (8, 13).

Statistical procedures used SigmaStat (Systat Software, Inc., San Jose, CA). Clinical and demographic data were described using medians, interquartile ranges, and frequencies. Comparisons between groups used the rank sum, chi-square, or Fisher's exact tests, as appropriate. The primary outcome variable for the regression procedures was all-cause 28-day mortality. Because persistent, multiple organ failure is a major antecedent of death secondary to sepsis, we also modeled a complicated course, defined as the persistence of two or more organ failures at Day 7 of septic shock or 28-day mortality (7–9).

RESULTS

Of the larger sepsis cohort, 67 met eligibility criteria. Twenty-three subjects were assigned to Endotype A, and 44 to Endotype B (Table 1). Subjects in Endotype A were younger with higher predicted mortality by both PRISM III and PERSEVERE. Subjects in Endotype A had 4-fold greater unadjusted 28-day mortality, and nearly 3-fold greater rates of complicated course. The association with mortality (OR 8.0, 95% CI 1.6 to 41.0) and complicated course (OR 4.2, 95% CI 1.2 to 14.9) persisted after adjustment for age, PRISM III score, and PaO_2/FIO_2 (Table 2). Cause of death was multiple organ dysfunction syndrome (MODS)(6).

DISCUSSION

Using our previously reported endotyping strategy in children with septic shock, we identified endotypes of AHRF secondary to sepsis. The endotypes had differential risk for mortality and complicated course, with Endotype A retaining an association with poor outcomes after adjustment for age, PRISM, and oxygenation. To our knowledge, this is the first demonstration of endotypes in pediatric AHRF. Our results support an investigation into using transcriptomics to identify mRNA-based endotypes in a dedicated, well-defined ARDS cohort.

The endotypes were initially derived from a septic shock cohort. However, Endotype A confers a two- to three-fold increased odds for mortality in the whole cohort with septic shock (6, 14, 15), whereas the association between Endotype A and mortality appears to be stronger in this AHRF subgroup. This may partly be due to the higher 28-day mortality rate of AHRF subjects (21%) versus the total septic shock cohort (8%), and it is possible that expression-based endotyping was more prognostic with greater severity of illness. Additionally, it is possible that the gene expression patterns which define the endotypes in sepsis also differentiate the underlying biology of respiratory failure, with better discrimination of mortality risk. As MODS is a shared mechanism of death for both sepsis and AHRF (16), the greater apparent association between Endotype A and mortality in AHRF may reflect common mechanisms associated with both AHRF and MODS.

Our study has limitations. This was an observational study, without protocolization of care, meaning outcomes may reflect management decisions independent of endotypes. Unlike studies of adult endotypes, we cannot guarantee subjects had ARDS, as chest radiographs

were not available and we could not ensure subjects had bilateral infiltrates; however, $PaO_2/FIO_2 \leq 200$ represents moderate/severe ARDS by Berlin criteria, and it is likely that we selected subjects with qualifying radiographic disease, but this cannot be proven. As the parent study was not a study of AHRF, detailed ventilator data and duration of ventilation were not collected. Furthermore, oxygenation index was unavailable, meaning we could not stratify subjects using 2015 Pediatric Acute Lung Injury Consensus Conference definitions of pediatric ARDS. Whole blood gene expression may not be the ideal compartment for AHRF classifications; however, it is far more accessible and feasible, as invasive bronchoalveolar sampling is uncommonly performed in pediatrics. Despite these limitations, the endotypes had strong associations with mortality and complicated course and retained independent association with outcomes after adjustment for confounders. Future studies will use genome-wide expression profiling and unsupervised hierarchical clustering of whole blood in a prospective cohort of pediatric ARDS to identify *de novo* endotypes. These current data demonstrated the presence of clinically relevant endotypes in AHRF with the potential for predictive enrichment for future clinical trials.

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Table 1:

Demographics of the AHRF subjects with septic shock

Variable	Endotype A	Endotype B
N (%)	23 (34)	44 (66)
Median Age, years (IQR)[a]	0.8 (0.1, 2.7)	4.3 (1.4, 7.2)
Males, n (%)	14 (64)	23 (52)
Median PRISM III score (IQR)[a]	22 (15, 30)	15 (9, 21)
PERSEVERE mortality probability (95% CI)[a]	0.227 (0.136 to 0.319)	0.101 (0.05 to 0.147)
PaO_2/FIO_2	78 (61, 131)	110 (76, 145)
No. with co-morbidity (%)	5 (22)	20 (41)
28-day mortality, n (%)[b]	10 (43)	4 (9)
Complicated Course, n (%)[c]	17 (74)	15 (27)

[a] $p < 0.05$ vs. endotype A, Rank Sum Test

[b] $p < 0.05$ vs. endotype B, Fisher Exact Test

[c] $p < 0.05$ vs. endotype B, Chi-square, 1 degree of freedom

Table 2:

Multivariable association of endotypes with mortality and complicated course

Variable	Odds ratio	95% CI	p value
Mortality			
Endotype A	8.0	1.6 to 41.0	0.013
PRISM III	1.1	1.0 to 1.2	0.005
Age	1.2	0.9 to 1.5	0.198
PaO_2/FIO_2	1.0	0.9 to 1.0	0.175
Complicated course			
Endotype A	4.2	1.2 to 14.9	0.026
PRISM III	1.1	1.0 to 1.1	0.013
Age	1.0	0.9 to 1.2	0.682
PaO_2/FIO_2	1.0	0.9 to 1.0	0.658