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Derivation, validation, and clinical relevance of a pediatric sepsis phenotype with persistent hypoxemia, encephalopathy, and shock

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OPEN

Derivation, Validation, and Clinical Relevance of a Pediatric Sepsis Phenotype With Persistent Hypoxemia, Encephalopathy, and Shock*

OBJECTIVES: Untangling the heterogeneity of sepsis in children and identifying clinically relevant phenotypes could lead to the development of targeted therapies. Our aim was to analyze the organ dysfunction trajectories of children with sepsis-associated multiple organ dysfunction syndrome (MODS) to identify reproducible and clinically relevant sepsis phenotypes and determine if they are associated with heterogeneity of treatment effect (HTE) to common therapies.

DESIGN: Multicenter observational cohort study.

SETTING: Thirteen PICUs in the United States.

PATIENTS: Patients admitted with suspected infections to the PICU between 2012 and 2018.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: We used subgraph-augmented nonnegative matrix factorization to identify candidate trajectory-based phenotypes based on the type, severity, and progression of organ dysfunction in the first 72 hours. We analyzed the candidate phenotypes to determine reproducibility as well as prognostic, therapeutic, and biological relevance. Overall, 38,732 children had suspected infection, of which 15,246 (39.4%) had sepsis-associated MODS with an in-hospital mortality of 10.1%. We identified an organ dysfunction trajectory-based phenotype (which we termed persistent hypoxemia, encephalopathy, and shock) that was highly reproducible, had features of systemic inflammation and coagulopathy, and was independently associated with higher mortality. In a propensity score-matched analysis, patients with persistent hypoxemia, encephalopathy, and shock phenotype appeared to have HTE and benefit from adjuvant therapy with hydrocortisone and albumin. When compared with other high-risk clinical syndromes, the persistent hypoxemia, encephalopathy, and shock phenotype only overlapped with 50%–60% of patients with septic shock, moderate-to-severe pediatric acute respiratory distress syndrome, or those in the top tier of organ dysfunction burden, suggesting that it represents a nonsynonymous clinical phenotype of sepsis-associated MODS.

CONCLUSIONS: We derived and validated the persistent hypoxemia, encephalopathy, and shock phenotype, which is highly reproducible, clinically relevant, and associated with HTE to common adjuvant therapies in children with sepsis.

KEY WORDS: critical care; organ dysfunction; pediatrics; precision medicine; sepsis

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***See also p. 869.**

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Sepsis is the most common cause of multiple organ dysfunction syndrome (MODS) in children, which in turn frequently leads to death (1–4). Although respiratory failure is the leading organ dysfunction associated with pediatric sepsis and sepsis-related deaths (5, 6), significant heterogeneity exists in the clinical presentation and underlying pathobiology of children with

RESEARCH IN CONTEXT

- Untangling the heterogeneity of pediatric sepsis and identifying clinically relevant phenotypes could lead to the development of more targeted therapies and improve outcomes in sepsis.
- Data-driven approaches have been used in adult sepsis studies and pediatric organ dysfunction studies to uncover phenotypes based on clinical trajectories with both prognostic and therapeutic implications.
- In this study, we derived and validated the persistent hypoxemia, encephalopathy, and shock phenotype, a high-risk phenotype of pediatric sepsis associated with heterogeneity of treatment effect to common adjuvant therapies.

sepsis (7, 8). Untangling the clinical and biological heterogeneity in sepsis and acute respiratory distress syndrome (ARDS) has been identified as a major research priority in the path toward precision medicine in critical care (9).

A major challenge for resolving the heterogeneity of sepsis stems from the reality that the pathobiology of septic patients is dynamic (10, 11). Oftentimes, single time points (such as ICU admission) are used to investigate this heterogeneity, but this approach fails to capture the critical importance of the evolving and dynamic nature of sepsis (12, 13). Data from electronic health records (EHRs) provides an attractive opportunity to perform data-driven analyses that incorporate the dimension of time by leveraging longitudinal clinical data from thousands of patients (10, 14). EHR data from adults with sepsis and children with MODS have been used to uncover subgroups of patients with similar clinical characteristics and trajectories (often called "phenotypes") that have been associated with clinically relevant findings, such as distinct cytokine profiles or heterogeneity of treatment effect (HTE) to interventions like balanced fluids or hydrocortisone administration (3, 15, 16). However, no prior study has used this approach to uncover trajectory-based phenotypes in a large cohort of children with sepsis.

In this study, we aimed to derive and validate clinically relevant sepsis phenotypes using a data-driven approach to analyze organ dysfunction trajectories in a large, multicenter cohort of children with sepsis-associated MODS. We hypothesized that we would identify one or more reproducible sepsis phenotypes based on the trajectories of organ dysfunctions in the acute phase of critical illness and that patients with similar trajectories would have similar risk factors, biochemical characteristics, responses to adjuvant therapies, and clinical outcomes.

METHODS

Study Design and Patient Population

This was a retrospective, multicenter, observational cohort study of children 0–18 years admitted to one of 13 participating US PICUs in the 6-year period between January 1, 2012, and January 1, 2018. Data for patients who had a confirmed or suspected infection (i.e., received systemic antimicrobials and microbiological testing in the ±24-hour time-window after admission to the PICU) were extracted from the EHRs of the participating institutions, which is consistent with prior studies of sepsis in hospitalized children (17, 18). The reporting of this observational cohort study was performed using the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline (19). The institutional review board (IRB) at Ann and Robert H. Lurie Children's Hospital of Chicago served as the central IRB for this study (IRB no. 2019-2481 "A Data-Driven Analysis of Pediatric Organ Dysfunction Patterns to Discover Novel Sepsis Phenotypes," approved on February 13, 2019, with a waiver of consent). Research procedures were performed in accordance with the institutional and federal ethical standards of human experimentation and with the Helsinki Declaration of 1975.

We measured the type, severity, and change in organ dysfunction using the six subscores of the pediatric Sequential Organ Failure Assessment (pSOFA) score (1). The pSOFA subscores were calculated for each 24-hour period between PICU admission and 72 hours, which was considered the acute phase of illness (14, 20). For missing data, individual pSOFA subscores were carried forward until they were remeasured or the patient died; otherwise, if completely missing they were assumed to be normal and the corresponding subscore was assigned a 0, as previously performed (21, 22). We defined patients with MODS as those with a pSOFA

subscore of greater than or equal to 2 in greater than or equal to 2 organ systems (3). For the trajectory-based phenotyping, we only included patients with sepsis-associated MODS, which were defined as those with confirmed or suspected infections on admission and MODS within 72 hours.

Trajectory-Based Phenotyping

Patients were split into three sets based on site, resulting in one derivation set (data from seven sites) and two external validation sets (three sites each), which is consistent with geographic-based external validation, an approach recommended by established guidelines for clinical model development and validation (23). We first used subgraph-augmented nonnegative matrix factorization (SANMF), an unsupervised trajectory modeling approach, to derive a set of organ dysfunction trajectory-based groups as candidate phenotypes in the derivation set, as previously performed (3). The SANMF analysis consisted of two parts: 1) subgraph mining, in which the individual trajectories of each of the six pSOFA subscores over the first 72 hours were analyzed to determine common patterns of severity and change of the individual organ dysfunctions across patients and 2) nonnegative matrix factorization, in which patients were grouped into candidate phenotypes based on similarity in the frequency of the subgraphs. The validation of these candidate phenotypes was then assessed using the framework described by DeMerle et al (24). Briefly, the validation of the candidate phenotypes was performed across three dimensions: 1) reproducibility of the candidate phenotypes in the first validation set using the SANMF mixture coefficient matrix to assess external validity; 2) reproducibility of the candidate phenotypes using different unsupervised trajectory modeling methods in the derivation and first validation set (using repeated measures latent class analysis [RM-LCA] and group-based trajectory modeling [GBTM]) to assess statistical validity; and 3) reproducibility of the candidate phenotypes in the second external validation set using a Random Forest classifier to assess whether the SANMF-based phenotypes groups can be accurately predicted in new datasets. The clinical relevance of the candidate phenotypes was also assessed across three dimensions: (1) prognostic relevance based on the independent association with outcomes; (2) therapeutic relevance based on the association with response to two adjuvant therapies (≥ 1 mg/kg IV hydrocortisone or ≥ 0.5 g/kg albumin in the first 24 hr); and (3) pathobiological relevance based on association with biochemical and clinical features linked to plausible disease mechanisms and other clinical syndromes. The adjuvant therapies studied were chosen a priori because they are commonly used in sepsis and have plausible mechanisms of action, but have conflicting evidence regarding their efficacy (5).

Additional details are included in eMethods (http://links.lww.com/PCC/C390).

RESULTS

Study Population

There were 38,732 children with suspected or confirmed infections on PICU admission. Of those, 15,246 (39.4%) had sepsis-associated MODS, of whom 1,537 (10.1%) died in the hospital. Sites contributed a median of 1,167 patients with sepsis-associated MODS (interquartile range [IQR] 837–1,596). The median unadjusted site-specific in-hospital mortality was 9.9% (IQR 8.2%–13.1%), which was significantly different across sites ($p < 0.001$). The **eTable 1** (http://links.lww.com/PCC/C390) presents the clinical characteristics and outcomes of patients with and without sepsis-associated MODS in the cohort. Children with sepsis-associated MODS were randomly split by site into a derivation set (7 sites with 7,503 patients), a first external validation set (3 sites with 3,484 patients), and a second external validation set (3 sites with 4,259 patients).

Derivation of Trajectory-Based Candidate Phenotypes Using SANMF

Subgraph mining uncovered 776 frequent subgraphs representing individual organ dysfunction trajectories. A total of 7,448 patients (99.3% of the derivation set) had at least one frequent subgraph and were included. In the SANMF analysis, patients were separated into four trajectory-based groups based on the cophenetic correlation and group size. Groups 1, 3, and 4 had an overall trajectory toward recovery of their organ dysfunctions (**Fig. 1**) and associated in-hospital mortalities in the 4.3%–6.3% range. Group 2 represented the only high-risk group with an in-hospital mortality of

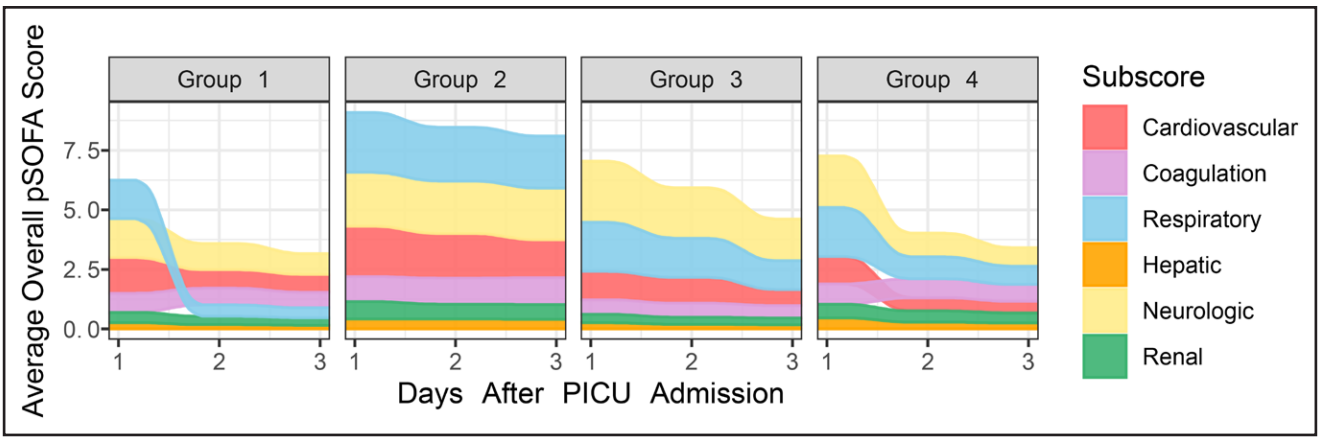

Figure 1. Alluvial plots of the four SANMF groups* based on the average daily pSOFA subscores. *Of note, group 2 was further characterized as the persistent hypoxemia, encephalopathy, and shock phenotype. SANMF = subgraph-augmented nonnegative matrix factorization; pSOFA = pediatric Sequential Organ Failure Assessment.

20.9% and was characterized by a trajectory of persistent respiratory, neurologic, and cardiovascular dysfunction in the first 72 hours (**eTable 2**, http://links.lww.com/PCC/C390).

Reproducibility of the Candidate Phenotypes

Applying the SANMF mixture coefficient matrix from the derivation set to the frequent subgraph counts of the first validation set demonstrated very reproducible distributions and associated clinical outcomes across the derivation and first validation sets (eTable 2, http://links.lww.com/PCC/C390). We then compared the overlap of the SANMF groups with the groups derived using RM-LCA and GBTM. Only SANMF group 2 had significant overlap with the groups derived by RM-LCA and GBTM (**eTable 3**, http://links.lww.com/PCC/C390). RM-LCA class 3 and GBTM group 4 had 78% and 79% overlap, respectively, with SANMF group 2. The agreement between the models for these overlapping groups was moderate (Fleiss' Kappa = 0.5, $p < 0.001$). All other overlaps ranged from 1% to 48% and had poor agreement.

Clinical Characterization and External Reproducibility Using a Classifier

SANMF group 2 was selected for further characterization as a sepsis phenotype because of its association with poor outcomes and its reproducibility. Based on the type, severity, and trajectory of the organ dysfunctions associated with the phenotype, we labeled it persistent hypoxemia, encephalopathy, and shock (**eFigure 1**, http://links.lww.com/PCC/C390).

We trained a Random Forest classifier on the derivation set using the pSOFA subscores for the first 3 days as features and the persistent hypoxemia, encephalopathy, and shock phenotype as the outcome. The classifier had an excellent performance at predicting the phenotype in the first validation set (area under the curve = 0.97; 95% CI, 0.96–0.97) (**eFigure 2**, http://links.lww.com/PCC/C390). When the model was applied to the second external validation set, patients classified as persistent hypoxemia, encephalopathy, and shock had a similar distribution, the severity of illness, and outcomes when compared with patients with the phenotype in the derivation set and first validation set, with some differences in the rate of comorbidities and organ support reflective of the populations in different sites (**eTable 4**, http://links.lww.com/PCC/C390). **Table 1** presents the demographics, clinical characteristics, and outcomes of patients with persistent hypoxemia, encephalopathy, and shock phenotype compared with patients with other sepsis-associated MODS in the entire cohort. Patients with the phenotype were younger, had higher severity of illness, received more organ support, and had worse outcomes. They were also slightly more likely to be categorized as "Other/Unknown" for the Race/Ethnicity classification when compared with "White, Non-Hispanic," and more likely to be admitted from the inpatient ward or directly to the PICU when compared with the emergency department.

Prognostic Relevance

In the mixed effects model, after adjusting for age, immunocompromised state, and mean pSOFA score

TABLE 1.

Clinical Characteristics of Children With the Persistent Hypoxemia, Encephalopathy, and Shock Phenotype and Those With Other Sepsis-Associated Multiple Organ Dysfunction Syndrome

Variables	Persistent Hypoxemia, Encephalopathy, and Shock (*n* = 4,836)	Other Sepsis-Associated MODS (*n* = 10,410)	
Age, yr (IQR)	4.3 (1–11.7)	5.2 (1.4–11.8)	< 0.001
Male, *n* (%)	2,637 (54.5)	5,742 (55.2)	0.478
Race/ethnicity, *n* (%)[a]			
White, non-Hispanic	2,279 (47.1)	5,127 (49.3)	0.009
Black, non-Hispanic	870 (18.0)	1,754 (16.8)	
Hispanic	875 (18.1)	1,966 (18.9)	
Asian	213 (4.4)	424 (4.1)	
Other/unknown	599 (12.4)	1,139 (10.9)	
Comorbidities, *n* (%)			
Immunocompromised	953 (19.7)	1,955 (18.8)	0.183
Technology dependent	2,166 (44.8)	4,733 (45.5)	0.445
Admission source, *n* (%)[b]			
Emergency department	2,000 (41.4)	4,789 (46.0)	< 0.001
Hospital floor	1,091 (22.6)	2,305 (22.1)	
Direct/transport	1,307 (27.0)	2,118 (20.3)	
Operating room	438 (9.1)	1,198 (11.5)	
Season, *n* (%)			
Spring	1,254 (25.9)	2,686 (25.8)	0.066
Summer	1,028 (21.3)	2,262 (21.7)	
Fall	1,063 (22.0)	2,442 (23.5)	
Winter	1,491 (30.8)	3,020 (29.0)	
Year, *n* (%)			
2012–2013	1,466 (30.3)	3,117 (29.9)	0.563
2014–2015	1,601 (33.1)	3,538 (34.0)	
2016–2017	1,769 (36.6)	3,755 (36.1)	
PRISM III score (IQR)	15 (10–23)	9 (5–14)	< 0.001
Organ support, *n* (%)			
Mechanical ventilation	3,787 (78.3)	5,940 (57.1)	< 0.001
Vasoactive infusion	3,348 (69.2)	2,844 (27.3)	< 0.001
Continuous renal replacement therapy	390 (8.1)	208 (2.0)	< 0.001
Extracorporeal membrane oxygenation	337 (7.0)	70 (0.7)	< 0.001

(*Continued*)

TABLE 1. (*Continued*)

Clinical Characteristics of Children With the Persistent Hypoxemia, Encephalopathy, and Shock Phenotype and Those With Other Sepsis-Associated Multiple Organ Dysfunction Syndrome

Variables	Persistent Hypoxemia, Encephalopathy, and Shock (*n* = 4,836)	Other Sepsis-Associated MODS (*n* = 10,410)	
Outcomes			
Length of stay, d (IQR)	15 (7–29)	9 (5–18)	< 0.001
Persistent MODS on day 7, *n* (%)	2,446 (50.6)	1,722 (16.5)	< 0.001
In-hospital mortality, *n* (%)	1,045 (21.6)	492 (4.7)	< 0.001

IQR = interquartile range; MODS = multiple organ dysfunction syndrome; PRISM III = Pediatric risk of mortality version 3.
[a]In a logistic regression model using the phenotype as the dependent variable and the race/ethnicity categories as independent variables with the "White, non-Hispanic" category as reference, the "Other/Unknown" category had a positive association with the phenotype ($p = 0.003$) when compared with "White, non-Hispanic" and after performing a Bonferroni correction for multiple comparisons.
[b]In a similar analysis as above using the Admission Source categories as independent variables with the "Emergency Department" category as reference, both the "Hospital Floor" category ($p = 0.006$) and the "Direct/Transport" category ($p < 0.001$) had a positive association with the phenotype when compared with the "Emergency Department" category and after performing a Bonferroni correction for multiple comparisons.

in the first 72 hours, the persistent hypoxemia, encephalopathy, and shock phenotype were associated with higher in-hospital mortality (adjusted odds ratio [aOR] = 4 [95% CI, 2.9–5.5]) and higher persistent MODS at 7 days (aOR= 2 [95% CI, 1.6–2.6]) (**eTable 5**, http://links.lww.com/PCC/C390). **eFigure 3** (http://links.lww.com/PCC/C390) presents the Kaplan-Meier survival curve.

Therapeutic Relevance

Overall, 14,983 patients survived for greater than 24 hours and were included in the propensity-matched (PSM) analysis. Patients who died before 24 hours were excluded to avoid survival bias (eMethods, http://links.lww.com/PCC/C390). The risk factors associated with a higher likelihood of receiving hydrocortisone or albumin were: age, immunocompromised status, admission source, pediatric risk of mortality version 3 score, vasoactive-inotropic score, and study site, which we included the PSM analysis (**eTables 6–8**, http://links.lww.com/PCC/C390). We matched 1,648 patients who received hydrocortisone (95%), and 1,162 patients who received albumin (100%) to untreated controls with similar propensity scores. Adequate covariate balance was achieved in both analyses (**eFigures 4** and **6**, http://links.lww.com/PCC/C390). We found a significant interaction between the persistent hypoxemia, encephalopathy, and shock phenotype and both hydrocortisone and albumin use: treated patients with the phenotype had lower mortality and less MODS at 7 days compared with patients with other sepsis-associated MODS (**Table 2**). The Kaplan-Meier curves of treated and matched controls are presented in **eFigures 5** and **7** (http://links.lww.com/PCC/C390).

In a sensitivity analysis including patients who died in the first 24 hours, the results were consistent with the findings in the main analysis (**eTable 9**, http://links.lww.com/PCC/C390). In a sensitivity analysis using Inverse Probability Treatment Weighting in the entire cohort with the same risk factors as in the PSM analysis, the interaction between the persistent hypoxemia, encephalopathy, and shock phenotype and hydrocortisone or albumin use was again associated with lower in-hospital mortality ($p < 0.001$).

Pathobiological Relevance

Patients with persistent hypoxemia, encephalopathy, and shock had more systemic inflammation, coagulopathy, and signs of hypoperfusion than patients with other sepsis-associated MODS (**Table 3**). Among the 689 patients (4.5%) who had a ferritin level obtained, the majority of patients with persistent hypoxemia, encephalopathy, and shock had hyperferritinemia, with more than half reaching levels greater than 1,000 ng/mL (Table 3).

TABLE 2.

Therapeutic Relevance Associated With the Persistent Hypoxemia, Encephalopathy, and Shock Phenotype Based on the Propensity Score Matched Analysis

Treatment and Outcomes	Matched Persistent Hypoxemia, Encephalopathy, and Shock Phenotype		Matched Other Sepsis-Associated MODS		*p* (Interaction)
Received hydrocortisone[a]	Yes (*n* = 772)	No (*n* = 770)	Yes (*n* = 876)	No (*n* = 878)	
Persistent MODS on day 7, *n* (%)	415 (53.8)	457 (59.4)	194 (22.1)	176 (20)	0.023
In-hospital mortality after 24 hr, *n* (%)	190 (24.6)	239 (31)	78 (9)	71 (8)	0.039
Received albumin[b]	Yes (*n* = 583)	No (*n* = 500)	Yes (*n* = 579)	No (*n* = 662)	
Persistent MODS on day 7, *n* (%)	337 (57.8)	305 (61)	163 (28.2)	136 (20.5)	0.003
In-hospital mortality after 24 hr, *n* (%)	143 (24.5)	168 (33.6)	53 (9)	47 (7)	0.004

MODS = multiple organ dysfunction syndrome.
[a]≥ 1 mg/kg of IV hydrocortisone in the first 24 hr.
[b]≥ 0.5 g/kg of albumin infusion in the first 24 hr.

When compared with other high-risk clinical syndromes in the first 72 hours of admission, the persistent hypoxemia, encephalopathy, and shock phenotype overlapped with 55% of patients meeting septic shock criteria, 54% of patients meeting moderate-to-severe pediatric ARDS criteria, and 62% of patient in the top tertile of organ dysfunction burden based on the mean pSOFA score (**eTable 10**, http://links.lww.com/PCC/C390; and **Fig. 2**).

DISCUSSION

In this study, we derived and validated the persistent hypoxemia, encephalopathy, and shock phenotype in children with sepsis-associated MODS. This trajectory-based sepsis phenotype had features of systemic inflammation and coagulopathy, was present in approximately one-third of children with sepsis-associated MODS, and was independently associated with mortality. Classification of this phenotype was reproducible in two external validation sets and using two alternative statistical methods for trajectory modeling. Additionally, in a propensity score analysis, patients with persistent hypoxemia, encephalopathy, and shock appeared to have a higher likelihood to benefit from adjuvant therapy with hydrocortisone and albumin when compared with other patients with sepsis-associated MODS. Finally, the persistent hypoxemia, encephalopathy, and shock phenotype overlapped with only about half of the patients with septic shock, half of those with moderate-to-severe pediatric ARDS, and less than two-thirds of those with the highest organ dysfunction burden based on the mean pSOFA score in the first 72 hours. These findings suggest that this phenotype does not simply describe the sickest patients or those recognizable as septic shock or ARDS

AT THE BEDSIDE

- Patients with persistent hypoxemia, encephalopathy, and shock phenotype appear to have heterogeneity of treatment effect to two common adjuvant therapies (hydrocortisone and albumin) but further research is warranted.
- Better understanding of the biological mechanisms associated with this high-risk phenotype could provide a foundation to develop novel targeted therapies.
- At the bedside, if we could accurately predict the organ dysfunction trajectory of children with sepsis, we could use that information for research purposes (e.g., enrollment in enriched clinical trials) and eventually for clinical decision-making (e.g., initiating targeted therapies).

TABLE 3.

Biochemical Characteristics of the Persistent Hypoxemia, Encephalopathy, and Shock Phenotype Compared With Other Sepsis-Associated Multiple Organ Dysfunction Syndrome

Variables	Patients With Values	Persistent Hypoxemia, Encephalopathy, and Shock (*n* = 4,836)	Other Sepsis-Associated MODS (*n* = 10,410)	*p*
Laboratory results, median (interquartile range)[a]				
Minimum absolute lymphocytes, K/μL	11,877	0.99 (0.43–1.81)	1.17 (0.54–2.14)	< 0.001
Minimum hemoglobin, g/dL	13,292	8.3 (7.1–9.7)	9.0 (7.5–10.5)	< 0.001
Maximum WBC, K/μL	12,812	12.9 (7.8–20.2)	11.20 (6.9–17)	< 0.001
Maximum bands, %	6,205	13 (5–25)	9 (3–19)	< 0.001
Maximum C-reactive protein, mg/dL	3,886	9.5 (3.3–22.9)	6.7 (2.5–18.3)	< 0.001
Maximum ferritin, ng/mL	689	1,102 (315–9,407)	435 (154–2,774)	< 0.001
Minimum platelets, K/μL	12,768	105 (42–199)	149 (63–238)	< 0.001
Maximum international normalized ratio	7,713	1.6 (1.3–2.1)	1.3 (1.2–1.7)	< 0.001
Maximum partial thromboplastin time, s	7,644	42 (33–68)	36 (30–47)	< 0.001
Maximum alanine aminotransferase, U/L	8,722	53 (27–161)	40 (23–91)	< 0.001
Maximum aspartate aminotransferase, U/L	8,639	86 (43–308)	54 (32–128)	< 0.001
Maximum total bilirubin, mg/dL	8,669	0.8 (0.3–2.3)	0.6 (0.3–2.1)	< 0.001
Minimum albumin, g/dL	10,067	2.4 (2.0–2.8)	2.6 (2.2–3.1)	< 0.001
Maximum blood urea nitrogen, g/dL	14,407	15 (9–26)	11 (7–18)	< 0.001
Maximum creatinine, g/dL	14,267	0.5 (0.3–0.9)	0.4 (0.3–0.6)	< 0.001
Maximum glucose, g/dL	14,225	196 (143–285)	148 (117–206)	< 0.001
Minimum pH	12,037	7.21 (7.10–7.29)	7.30 (7.23–7.35)	< 0.001
Minimum bicarbonate, mEq/L	14,584	19 (15–22)	21 (18–23)	< 0.001
Maximum lactate, mmol/L	9,294	2.9 (1.6–6.3)	1.8 (1.1–3.1)	< 0.001
Minimum Pao_2, mm Hg	6,726	63 (52–76)	74 (59–95)	< 0.001
Maximum $Paco_2$, mm Hg	6,726	55 (45–68)	46 (40–54)	< 0.001

MODS = multiple organ dysfunction syndrome, $Paco_2$ = partial pressure of arterial carbon dioxide, Pao_2 = partial pressure of arterial oxygen.

[a]Minimum or maximum value within 72 hr of admission, as indicated.

by clinicians, but rather it represents a nonsynonymous phenotype that combines features of those syndromes and is associated with the majority (almost 70%) of all deaths in this cohort.

Prior studies have identified phenotypes with characteristics similar to persistent hypoxemia, encephalopathy, and shock phenotype. Knox et al described the shock with hypoxemia and altered mental status phenotype and Seymour et al described the γ phenotype in adult sepsis patients, which share similar features, including hypoxemia, vasoactive dependence, inflammation, and high mortality (12, 13). The γ phenotype has been found to be predominant in patients with pneumonia, which is a common etiology of sepsis in children (25). Calfee et al and Dahmer et al have also described a hyperinflammatory phenotype of ARDS in adults and children, respectively, which share common features with the phenotype we describe here (26, 27). Similar to our findings, the hyperinflammatory ARDS phenotype is commonly associated with more sepsis, inflammation, hypotension, and coagulopathy than other patients with ARDS (26–28). Importantly, Calfee et al have shown that the hyperinflammatory ARDS phenotype is associated with

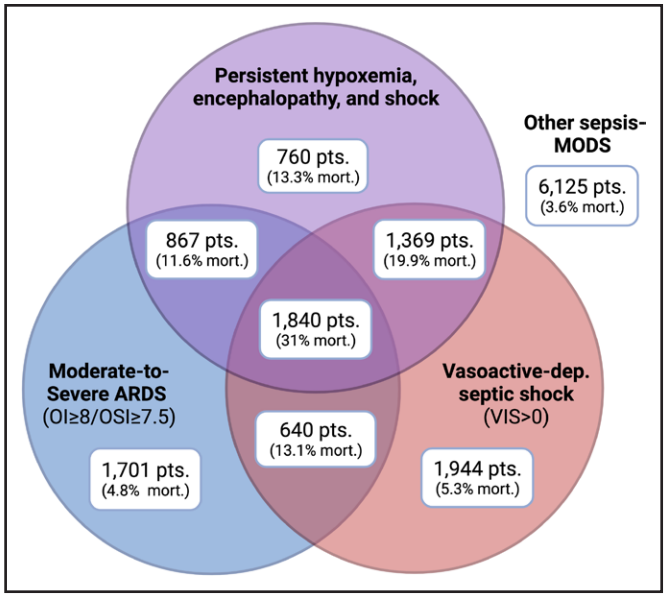

Figure 2. Venn diagram of the overlap of persistent hypoxemia, encephalopathy, and shock with vasoactive-dependent septic shock and moderate-to-severe pediatric ARDS among patients with sepsis-associated MODS*. *Among patients with sepsis-associated MODS, there were a total of 5,048 patients with moderate-to-severe ARDS (16.6% mortality), 5,793 with vasoactive-dependent septic shock (17.8% mortality), and 4,836 with persistent hypoxemia, encephalopathy, and shock (21.6% mortality). ARDS, acute respiratory distress syndrome; dep. = dependent; MODS = multiple organ dysfunction syndrome; mort. = in-hospital mortality; OI = oxygenation index; OSI = oxygen saturation index.

HTE to ventilator strategies and fluid management (26, 29, 30). Additionally, our group has previously derived and validated a high-risk phenotype with persistent hypoxemia and shock in children with MODS (both with and without sepsis) that also appeared to have HTE to hydrocortisone in a two-center study (3), and a shock trajectory group that we termed "moderate, prolonged shock" that was enriched for patient with sepsis (31). Finally, Carcillo et al have described the hyperferritinemic response in sepsis as a distinct, high-risk phenotype characterized by macrophage activation that is potentially susceptible to anti-cytokine therapy (8, 32–34), and Horvat et al demonstrated that the subset of septic children with persistent hyperferritinemia and elevated C-reactive protein has the highest mortality (35). Importantly, macrophage activation appears to be a key mechanism in sepsis-related lung injury (36–39).

In our two-center MODS phenotype study, 72% of patients with persistent hypoxemia and shock met the criteria for sepsis-associated MODS (724 of 1,012) which was higher than in the other groups (where only 57% met sepsis-associated MODS criteria) (3). Whether the HTE associated with hydrocortisone in that phenotype was driven by patients with sepsis and persistent hypoxemia and shock or if the organ dysfunction trajectory alone was enough to explain this association remains unclear, but it is an important question. On a related note, Villar et al(40) performed an enrichment strategy in their ARDS randomized controlled trial by only enrolling adult patients who had persistent hypoxemia 24 hours after initial ARDS diagnosis (of which 77.3% met criteria for sepsis and/or pneumonia) and they found that patients who met that persistent hypoxemia criterion and received dexamethasone had significantly lower mortality than controls.

Our findings have important implications. Although risk stratifying critically ill children with infections and sepsis early in the course is important for diagnostic purposes, the clinical reality is that most children with sepsis will suffer their worst degree of MODS on the day of admission and most will tend to follow a trajectory of recovery after admission, as observed our and previous studies (4, 41). Thus, understanding which children with sepsis will have a trajectory of persistent or worsening organ dysfunction, what patterns of dysfunction are expected in those children, and why they display those patterns from a pathobiological standpoint, become questions of paramount importance. In our study, we have identified a high-risk, highly reproducible trajectory-based phenotype of pediatric sepsis with both prognostic and therapeutic relevance. However, the persistent hypoxemia, encephalopathy, and shock phenotype require longitudinal information for patient classification. For this type of classification to be clinically useful, it would need to be predicted earlier in the clinical course. Prediction of phenotype membership is the next, important step in this line of research and could be performed through a combination of machine learning approaches using EHR data (42), biomarkers (43), and physiological markers like heart rate variability, which is associated with proinflammatory states (44, 45).

Our study has several strengths and limitations. We performed our analysis using a large, granular, multicenter cohort with wide geographic and racial-ethnic representation of children in the United States,

which is the largest published cohort of its kind in pediatric sepsis. Furthermore, we derived and validated the persistent hypoxemia, encephalopathy, and shock phenotypes using data that was partitioned by study sites, which allowed us to test the external validity and generalizability of the phenotype. However, our dataset was observational in nature and susceptible to selection bias and the uncertainty introduced by missing data. Although we used standard approaches to ensure data quality, deal with missing data, and adjust for confounders, further validation of our findings is needed. For example, it is possible that the imputation approach we used could underestimate or overestimate the degree of organ dysfunction in some patients, especially those dependent on laboratory tests. Furthermore, there may be patients with chronic organ dysfunctions (e.g., static encephalopathy with low baseline Glasgow Coma Scale [GCS]) that would be considered as having MODS if a second organ dysfunction is present. Similarly, low GCS may be reflective of critical illness-related interventions (e.g., sedation, neuromuscular blockade) and not necessarily a primary organ dysfunction. Additionally, our criteria for confirmed or suspected infection excluded children with viral-only infections that never received antimicrobials, which could limit the generalizability of the results to that population. However, it is likely that even in cases of viral sepsis, patients would have received empiric antibiotic therapy until a bacterial or fungal coinfection was ruled out. Furthermore, we have focused our analysis on persistent hypoxemia, encephalopathy, and shock; however, it is very likely that other subgroups with prognostic and therapeutic relevance exist among other patients with sepsis-associated MODS, but either the granularity and type of data included in this study or the modeling approaches we used were unable to uncover these subgroups. Further studies using more granular data as well as other dimensions of patient information (e.g., molecular, physiological) and modeling approaches are needed. Finally, our therapeutic relevance analysis using propensity scoring is susceptible to residual confounding by unmeasured confounders and must be interpreted with caution (46).

In conclusion, we derived and validated the persistent hypoxemia, encephalopathy, and shock phenotype, a high-risk trajectory-based organ dysfunction phenotype that is associated with HTE to common adjuvant therapies. Future studies are needed to ascertain the reproducibility of this phenotype, assess whether it can be predicted earlier in the course, further study the possible biological mechanisms underlying it, and investigate candidate therapeutic targets.

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