Morbidity and Mortality in Critically Ill Children. I. Pathophysiologies and Potential Therapeutic Solutions*

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Objectives: Developing effective therapies to reduce morbidity and mortality requires knowing the responsible pathophysiologies and the therapeutic advances that are likely to be impactful. Our objective was to determine at the individual patient level the important pathophysiological processes and needed therapeutic additions and advances that could prevent or ameliorate morbidities and mortalities.

Design: Structured chart review by pediatric intensivists of PICU children discharged with significant new morbidity or mortality to determine the pathophysiologies responsible for poor outcomes and needed therapeutic advances.

Setting: Multicenter study (eight sites) from the Collaborative Pediatric Critical Care Research Network of general and cardiac PICUs.

Patients: First PICU admission of patients from December 2011 to April 2013.

Interventions: None.

Measurements and Main Results: Two-hundred ninety-two patients were randomly selected from 681 patients discharged with significant new morbidity or mortality. The median age was 2.4 years, 233 (79.8%) were in medical/surgical ICUs, 59 (20.2%) were in cardiac ICUs. Sixty-five (22.3%) were surgical admissions. The outcomes included 117 deaths and 175 significant new morbidities. The most common pathophysiologies contributing to the poor outcomes were impaired substrate delivery ($n = 158$, 54.1%) and inflammation ($n = 104$, 35.6%). There were no strong correlations between the pathophysiologies and no remarkable clusters among them. The most common therapeutic needs involved new drugs ($n = 149$, 51.0%), cell regeneration ($n = 115$, 39.4%), and immune and inflammatory modulation ($n = 79$, 27.1%). As with the pathophysiologies, there was a lack of strong correlations or meaningful clusters in the suggested therapeutic needs.

Conclusions: There was no single dominant pathophysiology or cluster of pathophysiologies responsible for poor pediatric critical care outcomes. Therapeutic needs often involved therapies that are not close to implementation such as cell regeneration, improved organ transplant, improved extracorporeal support and artificial organs, and improved drugs. (*Crit Care Med* 2020; 48:790–798)

Key Words: morbidity; mortality; pediatric critical care; pediatrics; research; research agenda

Effective therapeutic advances to reduce pediatric critical care morbidity and mortality are often directed at the pathophysiological cause, traditionally classified by diagnostic classifications or the primary system of dysfunction (1–5). Yet, traditional classification systems may lack meaningful pathophysiological relationships to adverse outcomes. For example, morbidity and mortality may be associated with secondary symptom complexes such as respiratory distress syndrome that have multiple pathophysiological triggers, each of which might be responsible for the adverse outcome (6). Adverse outcomes may also be secondary to pathophysiologies not captured by the acute diagnosis such as underlying conditions or complications of medications. Conditions such as sepsis involve multiple pathophysiological processes, each potentially responsible for adverse outcomes (7, 8).

Research agendas are developed to derive a future benefit from an investment of research time and dollars. Both formal and informal processes have been used to develop research agendas, but the agenda-setting process has primarily focused on integrating the knowledge and values of content experts (9, 10), especially for critical care (11–13). If the experts have insufficient or inaccurate information or if they are overly committed

*See also p. 921.

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to a specific issue, the final agenda may not reflect the most productive path.

There has not been an effort in pediatric critical care to identify a research agenda that would maximally reduce morbidity and mortality. To inform such an agenda, the Collaborative Pediatric Critical Care Research Network (CPCCRN) prioritized the identification of pathophysiologies responsible for new morbidities and mortality and the therapeutic advances that might ameliorate or prevent these adverse outcomes. The primary aims of this initiative, Informing the Research Agenda, were to determine the following at the individual patient level which could improve clinical outcomes: 1) the important pathophysiological processes resulting in morbidity and mortality and 2) needed therapeutic additions and advances that could prevent or ameliorate morbidity and mortality. Importantly, we investigated this aim at the individual patient level with structured chart reviews rather than using expert opinion or diagnostic lists. Secondary aims included: 1) the development of classification schemes for important pathophysiological processes and needed therapeutic additions and advances, and 2) the development of a generalizable structured chart review methodology appropriate for the primary aim and applicable to other medical issues. The chart review methodology has been published (14). This analysis focuses on the overall assessment of pathophysiologies and needed therapeutic advances. A companion analysis focuses on the specific issues identified at the patient level (15).

MATERIALS AND METHODS

Patients

The patients for this analysis originated in the Trichotomous Outcome Prediction in Critical Care (TOPICC) study conducted by CPCCRN. Data collection methods and institutional characteristics have been previously described (16). There were seven funded sites, one being composed of two institutions. In brief, patients aged from newborn to less than 18 years were randomly selected and stratified by hospital from December 4, 2011, to April 7, 2013. Patients from both general-medical and cardiac-cardiovascular PICUs were included. Only the first PICU admission during a hospitalization was included. The protocol was approved by all Institutional Review Boards.

Patients discharged with a significant new morbidity or who died during their hospitalization were eligible for inclusion. A significant new morbidity was defined as an increase in the Functional Status Scale (FSS) score of 2 or more in a single functional domain from their preillness baseline (17, 18). The previous definition of a significant new morbidity was an FSS increase of 3 or more. Since 95.4% of those patients had an increase of at least two in a single domain, we adopted that simpler and more conservative definition for this analysis (18). New morbidities were classified as moderate (FSS = 9–13), severe (FSS = 14–20), and very severe (FSS = > 20) (18). Mortalities were included if they were potentially savable at admission as indicated by a mortality risk of less than 80% (19). Eligible patients at each clinical site were randomized by the data coordinating center and reviewed in the randomization sequence until 25 or more patients per site were evaluated.

Structured Chart Review

We developed a time-limited, structured chart review method based on methods initially developed for the assessment of safety and quality of healthcare (20–22). The method, validity, reliability, and reviewer qualifications have been published (14). In brief, reviewers at each site (third year critical care fellows or attendings) read the study protocol, attended a small group, web-based session which included the study overview, the structured chart review process, and the electronic data capture system, and conducted 2–4 initial reviews with one of the project co-principal investigators (M.M.P., K.L.M.) who served as central reviewers. The review was intended to take an average of 30 minutes per case. For each subsequent case review, the site reviewer went over their assessments with a central reviewer to maintain consistency in the classifications across sites. During this process, the reviewers confirmed the data collected in the TOPICC project and assessed the classification for the pathophysiologies and therapies (below).

Categorizing Pathophysiological Processes, and Needed Therapeutic Additions or Advances

We anticipated that developing meaningful classification systems for the primary aims might be challenging. First, causes of morbidity and mortality are often conditions or symptom complexes (e.g., respiratory distress syndrome) that have many etiologies (6). Second, symptom complexes often lack specificity because they were sometimes chosen for a high sensitivity and low specificity (e.g., systemic inflammatory response syndrome) (23). Third, even when the diagnosis is known, critical care diagnoses may have several potential pathophysiological processes. For example, sepsis has multiple clinical phenotypes and pathophysiological processes that have different prognostic and therapeutic significance (7, 8). Fourth, the events and pathophysiological processes most immediately associated with the adverse outcome may not be the underlying cause of the outcome that, if it had been interrupted, would have ameliorated or prevented the outcome. Finally, adverse outcomes may be related to complications of care that may not be captured by the acute diagnosis (24, 25).

We used free listing to determine the classification schema for the pathophysiological process, and needed interventions and life support technologies (26–28). Free listing, a qualitative research technique, requires the recognition of the "domains of interest" (pathophysiological processes, therapeutic advances) and the use of an expert group to choose the content, scope, and domain structure. Free listing was used as an iterative process with CPCCRN Steering Committee over three sessions. The CPCCRN Steering Committee consisted of PIs, co-PIs, and alternate PIs for the investigative sites, the data coordinating center, and representatives of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development with expertise relevant

to this project. An iterative process with inter-current analytic summaries was used. Briefly, each individual was asked to list all pathophysiologies potentially contributing to morbidity or mortality in PICUs. Each item on each list was typed on a card. Next, cards were sorted into piles representing the same or similar pathophysiologies. The results were presented to the group and each individual was asked to suggest items to add, delete, or combine. The suggestions were organized by placing similar suggestions together. The authors (M.M.P., K.L.M.) independently revised the list of pathophysiologies based on the group's suggestions and then compared their revisions. Through review and discussion, the final list of main pathophysiologic categories was generated. The category "other" was added to capture additional pathophysiologies that might be identified during the medical record review (**Table 1**). A similar process of free listing and pile sorting was used to generate the list of major therapeutic additions and advances (**Table 2**).

The reviewers recorded the process(es) and subprocess(es) occurring for each patient to support their conclusion and these were reviewed with the co-PIs. Additionally, the reviewers and co-PIs recorded if a chronic condition (29) contributed to the morbidity or mortality.

Data

Descriptive data have been described (16). Morbidity was determined with the FSS, and severity of illness was characterized using the Pediatric Risk of Mortality (PRISM) score (19).

Each reviewer confirmed the patient data consisting of age, baseline, and hospital discharge functional status and the admission and discharge dates. Since the functional status in the TOPICC database was obtained using information from the bedside caregivers as well as the medical record, we expected that some of the TOPICC morbidity data would not be confirmed using the medical record. If the morbidity could not be confirmed, the patient was excluded.

Multiple pathophysiologies and needed therapeutic additions or advances could be selected for each patient. Additionally, both the site and central reviewers constructed pathophysiological sequences for the morbidity or mortality. After all reviews were completed, the central reviewers reviewed all cases together to further ensure consistency in the classifications.

TABLE 1. Pathophysiology Categories

Impaired substrate delivery
Oxygen (hypoxia)/blood/other
Coagulation dysfunction
Thrombotic disorders—congenital/acquired
Thrombotic disorder—clinical (platelet/clotting factors/other)
Bleeding disorder—congenital/acquired
Bleeding disorder—clinical (platelet/clotting factors/other)
Other
Inflammation
Infection with organism
Oxidative injury (acute or chronic)
Oxidative injury (molecular mechanism)
Other
Immune dysfunction
Function increased/decreased/other
Toxicities
Drugs/endogenous substances/electrolytes/other
Tissue injury (direct)
Trauma/burns/other
Malnutrition
General malnutrition/other
Electrical signaling dysfunction
Neurologic/cardiac/other
Abnormal growth/abnormal cell cycle
Malignancy/disorders of apoptosis/disorders of necrosis
Capillary/vascular dysfunction
Capillary leak syndrome/other
Mitochondrial dysfunction
Other

The primary pathophysiology is followed by the diagnostic categories.

Statistics

Summaries for continuous variables use medians (Q1–Q3), whereas categorical summaries are presented using counts and percentages. To assess the differences among included and excluded patients, the Wilcoxon rank-sum test was used to compare age, PRISM, and baseline FSS. Categorical variables are compared using Fisher exact test. For patients surviving to hospital discharge, the Cochran-Armitage trend test was used to assess any directional tendency in dysfunction severity at hospital discharge. Cluster analysis approaches using the single linkage method as implemented in the R function hclust (30) were used to display relationships within and between pathophysiologies, chronic conditions, and therapeutic conditions and advances. The Canberra distance metric (31) was used for clustering of pairwise count data, whereas standard Euclidean distance was used for clustering of Spearman correlations. Dendrograms summarizing relationships between factors were constructed using the Euclidean distance metric with the heat map function. Graphical displays of matrices and dendrograms were generated using the R packages reshape2 (32) and ggplot2 (33). The matrices and dendrograms presented should not necessarily be construed as "best" or optimal summaries of associations, but rather as guides to identifying relatively similar and dissimilar factors.

RESULTS

Of 10,078 children in the TOPICC study, 681 had a significant new morbidity or mortality at hospital discharge. Among

TABLE 2. Therapeutic Interventions and Advances

Mechanical respiratory support
Inhaled respiratory support
Renal replacement and plasmapheresis
Extracorporeal support and artificial organs
Extracorporeal oxygenation
Extracorporeal circulatory support
Other
Organ transplant
Blood and blood products
Drugs
Drug delivery
Immune and inflammatory modulation
Nutritional support
Therapeutic devices
Defibrillator
Nerve stimulator
Stents
Temperature regulation
Vascular access
Ventricular drains
Other
Monitoring devices
Brain oxygenation
Cardiac output
Cellular metabolism
Electroencephalogram
Intracranial pressure
Regional blood flow (specify region)
Substrate utilization (i.e., oxygen, glucose, other)
Gas exchange (i.e., transcutaneous)
Other
Cell regeneration
Suspended animation
Mitochondrial support
Other

these patients, 327 were randomly selected for chart review. Thirty-five patients (10.7%) were excluded because data could not be confirmed (**Supplemental Table 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/F417). Although age, sex, and discharge FSS scores did not differ between the included and excluded samples, the excluded sample had lower mortality rates (2.9% vs 40.1%; $p < 0.001$) and PRISM scores (2.0 [0.0–10] vs 7.0 [0.5–14.0]; $p < 0.009$). The differences in mortality rates and PRISM scores were expected because the primary exclusion criterion was the inability to confirm the discharge FSS which was only present in survivors.

The sample characteristics of the 292 included patients are shown in **Table 3**. The median age was 2.4 years, 55.5% were male, 79.8% were in combined medical/surgical ICUs, 20.2% were in cardiac ICUs, 22.3% were surgical admissions, and their median PRISM score was 7.0. The outcomes included 40.1% mortality and 59.9% new morbidity rates. A total of 65.1% of the survivors were discharged with moderate functional disability (change in FSS of 4.0), 25.1% with severe disability (change in FSS of 7.5), and 9.7% with very severe disability (change in FSS of 15.0).

The pathophysiologies responsible for morbidities and mortalities are shown in **Table 4**. Overall, there were 2.9 ± 1.4 pathophysiologies/patient. Impaired substrate delivery ($n = 158$, 54.1%), inflammation (35.6%), and direct tissue injury (21.9%) were the most common with all other pathophysiologies except mitochondrial dysfunction present in greater than 10% of cases. The highest mortality rates were observed in patients with coagulation dysfunction (61.5%), impaired substrate delivery (58.9%), vascular/capillary dysfunction (55.8%), and immune dysfunction (53.1%). The PRISM score hierarchy was similar. The highest morbidity rates were in those with toxicities (72.5%), malnutrition (72.2%), and electrical signaling (69.2%) categories. Chronic conditions contributed to the morbidity or mortality in 156 children (53.4%) and had an associated mortality rate of 45.5%. Impaired substrate delivery, capillary/vascular dysfunction, and coagulation dysfunction were more frequently ($p < 0.05$) associated with mortality than morbidity (**Supplemental Table 2**, Supplemental Digital Content 2, http://links.lww.com/CCM/F418).

There was a lack of strong pairwise associations between the pathophysiologies. The two most frequent pathophysiology pairs were impaired substrate delivery and inflammation ($n = 57$), and capillary and vascular dysfunction and impaired substrate delivery ($n = 38$) (**Supplemental Fig. 1**, Supplemental Digital Content 3, http://links.lww.com/CCM/F419; **legend**, Supplemental Digital Content 9, http://links.lww.com/CCM/F425). Similarly, there were few strong associations between the pathophysiologies (**Supplemental Fig. 2**, Supplemental Digital Content 4, http://links.lww.com/CCM/F420; legend, Supplemental Digital Content 9, http://links.lww.com/CCM/F425). The highest positive Spearman correlation coefficients were between immune dysfunction and inflammation ($r = 0.34$) with other weak positive correlations between vascular/capillary dysfunction and impaired substrate delivery ($r = 0.18$), and coagulation dysfunction and impaired substrate delivery ($r = 0.18$). The highest negative correlation occurred between abnormal growth/abnormal cell cycle and direct tissue injury ($r = –0.18$). The dendrogram cluster analysis was consistent with these associations with no pairs or clusters of strong similarity (**Supplemental Fig. 3**, Supplemental

TABLE 3. Characteristics of the 292 Patients

Characteristic	Overall (*n* = 292)
Age at PICU admission, yr, median (IQR)	2.4 (0.4–9.5)
Sex, *n* (%)	
Male	162 (55.5)
Female	130 (44.5)
Race, *n* (%)	
White	135 (46.2)
Black	78 (26.7)
Other/unknown	79 (27.1)
Ethnicity, *n* (%)	
Hispanic or Latino	54 (18.5)
Not Hispanic or Latino	198 (67.8)
Unknown or not reported	40 (13.7)
Elective/emergency status, *n* (%)	
Elective	59 (20.2)
Emergency	233 (79.8)
Admission category[a], *n* (%)	
Postintervention—cardiac	35 (12.0)
Postintervention—noncardiac	30 (10.3)
Medical admission (nonintervention)	227 (77.7)
Admission source, *n* (%)	
Operating room/postanesthesia recovery unit	65 (22.3)
Inpatient unit from same hospital	57 (19.5)
Direct admission from other hospital	84 (28.8)
Emergency department	86 (29.5)
Payer, *n* (%)	
Commercial	99 (33.9)
Government	169 (57.9)
Other	24 (8.2)
PICU type, *n* (%)	
Cardiac	59 (20.2)
Medical/surgical/other	233 (79.8)
PICU length of stay, d, median (IQR)	8.9 (2.8–22.2)
Hospital length of stay, d, median (IQR)	20.8 (8.2–45.4)
Baseline Functional Status Scale score, median (IQR)	6.0 (6.0–8.0)
Pediatric Risk of Mortality score, median (IQR)	7.0 (0.5–14.0)
Discharge outcome, *n* (%)	
Died	117 (40.1)
Morbidity[b]	175 (59.9)
Moderate dysfunction	114 (65.1)
Severe dysfunction	44 (25.1)
Very severe dysfunction	17 (9.7)

IQR = interquartile range.

[a]Intervention includes operations and interventional catheterizations.

[b]Functional Status Scale categories for dysfunction: moderate = 9–13; severe = 14–20; very severe = > 20. Percentages of the morbidity categories refer to survivors.

Digital Content 5, http://links.lww.com/CCM/F421; legend, Supplemental Digital Content 9, http://links.lww.com/CCM/F425).

The proposed therapeutic additions and advances are shown in Table 4. Overall, there were 2.3 ± 1.2 therapeutic additions and advances/patient identified. Because this tabulation was unique, we expected that some of the categories might not be frequently selected. The most common suggested advances involved new drugs (*n* = 149, 51.0%), cell regeneration (*n* = 115, 39.4%), and immune and inflammatory modulation (*n* = 79, 27.1%). One category was not selected (drug delivery methods) and seven were selected in less than 10% of the cases. The highest death rates occurred in the categories of renal replacement and plasmapheresis (75.0%), extracorporeal support and artificial organs (70.2%), and organ transplant (70.2%).

Similar to the pathophysiological processes, there was a lack of strong pairwise association between the therapeutic additions and advances. Only two pairs had at least 40 occurrences, new drugs and cell regeneration (*n* = 47), and new drugs and immune and inflammatory modulation (*n* = 46) (**Supplemental Fig. 4**, Supplemental Digital Content 6, http://links.lww.com/CCM/F422; legend, Supplemental Digital Content 9, http://links.lww.com/CCM/F425). Similarly, there were few strong associations (**Supplemental Fig. 5**, Supplemental Digital Content 7, http://links.lww.com/CCM/F423; legend, Supplemental Digital Content 9, http://links.lww.com/CCM/F425) with the highest positive correlations between extracorporeal support and artificial organs and organ transplant (*r* = 0.39), mitochondrial support and renal replacement and plasmapheresis (*r* = 0.27), and immune and inflammatory modulation and renal replacement and plasmapheresis (*r* = 0.23). The highest negative correlation occurred between organ transplant and cell regeneration (*r* = –0.22). The dendrogram cluster analysis (**Supplemental Fig. 6**, Supplemental Digital Content 8, http://links.lww.com/CCM/F424; legend, Supplemental Digital Content 9, http://links.lww.com/CCM/F425) indicated that six categories were relatively similar: suspended

TABLE 4. Pathophysiologies and Needed Therapeutic Additions and Advances

Variable	*n* (%)	Age, yr[a]	Deaths, *n* (%)[b]	Pediatric Risk of Mortality Score[a]
Pathophysiologies				
Impaired substrate delivery	158 (54.1)	1.5 (0.3–7.8)	93 (58.9)	11.0 (3.0–19.0)
Inflammation	104 (35.6)	3.5 (0.7–11.1)	47 (45.2)	5.0 (0.0–12.0)
Tissue injury	64 (21.9)	4.5 (1.0–10.6)	25 (39.1)	8.0 (3.0–16.0)
Electrical signaling dysfunction	52 (17.8)	1.6 (0.4–8.0)	16 (30.8)	5.0 (0.0–13.5)
Abnormal growth/abnormal cell cycle	52 (17.8)	2.9 (0.5–7.5)	22 (42.3)	6.0 (0.0–12.0)
Capillary/vascular dysfunction	52 (17.8)	2.3 (0.5–8.7)	29 (55.8)	7.0 (2.5–15.0)
Toxicities	51 (17.5)	3.1 (0.5–10.3)	14 (27.5)	7.0 (0.0–16.0)
Immune dysfunction	49 (16.8)	10.1 (3.0–13.7)	26 (53.1)	8.0 (1.0–13.0)
Coagulation dysfunction	39 (13.4)	2.2 (0.4–12.6)	24 (61.5)	9.0 (3.0–19.0)
Malnutrition	36 (12.3)	1.1 (0.2–4.5)	10 (27.8)	3.5 (0.0–8.0)
Mitochondrial dysfunction	5 (1.7)	0.7 (0.5–13.7)	2 (40.0)	7.0 (6.0–12.0)
Other	19 (6.5)	1.2 (0.2–12.8)	6 (31.6)	6.0 (3.9–12.0)
Needed therapeutic additions/advances[c]				
Drugs	149 (51.0)	3.1 (0.5–9.5)	57 (38.3)	6.0 (0.0–13.0)
Cellular regeneration	115 (39.4)	3.1 (0.4–10.4)	39 (33.9)	9.0 (3.0–18.0)
Immune and inflammatory modulation	79 (27.1)	7.0 (1.4–13.4)	39 (49.4)	7.0 (2.0–14.0)
Extracorporeal support and artificial organs	47 (16.1)	0.6 (0.0–4.9)	33 (70.2)	10.0 (3.0–18.0)
Organ transplantation	47 (16.1)	1.9 (0.2–10.1)	33 (70.2)	10.0 (3.0–15.0)
Mechanical respiratory support	41 (14.0)	1.7 (0.7–9.5)	16 (39.0)	5.0 (0.0–12.0)
Nutritional support	39 (13.4)	1.1 (0.2–4.7)	10 (25.6)	4.0 (0.0–8.0)
Therapeutic devices	28 (9.6)	0.8 (0.2–5.4)	15 (53.6)	7.5 (3.0–17.5)
Monitoring devices	28 (9.6)	2.2 (0.3–7.9)	13 (46.4)	7.5 (0.5–21.5)
Blood and blood products	9 (3.1)	4.3 (1.4–12.6)	6 (66.7)	13.0 (5.0–20.0)
Renal replacement therapy and plasmapheresis	8 (2.7)	6.5 (3.5–15.8)	6 (75.0)	7.0 (2.5–17.0)
Mitochondrial support	6 (2.1)	0.6 (0.4–13.7)	3 (50.0)	6.5 (2.0–12.0)
Inhaled respiratory support	5 (1.7)	3.0 (0.6–11.1)	0 (0.0)	2.0 (1.0–4.0)
Suspended animation	2 (0.7)	0.6 (0.4–0.7)	2 (100.0)	14.5 (3.0–26.0)
Other	92 (31.5)	2.3 (0.4–9.3)	40 (43.5)	7.0 (1.0–13.0)

[a]Median (interquartile range [quartile 1–quartile 3]).
[b]The reported death rate is out of those with the specific therapy.
[c]Drug delivery methods were not selected.

animation, drug delivery, mitochondrial support, inhaled respiratory support, renal replacement and plasmapheresis, and blood and blood products, primarily because they were very infrequently chosen.

Figure 1 shows the cluster analysis for both the pathophysiological processes and proposed therapeutic additions and advances. Several of the pathophysiologies and therapeutic additions and advances show the expected pairwise similarities including malnutrition and nutritional support, transplantation and extracorporeal support/artificial organs, and immune dysfunction and immune and inflammatory modulation. The most similar cluster of items included suspended animation, drug delivery, inhaled respiratory support, renal replacement and plasmapheresis, mitochondrial dysfunction and support, and blood products but their similarities were primarily a result of their lack of selection.

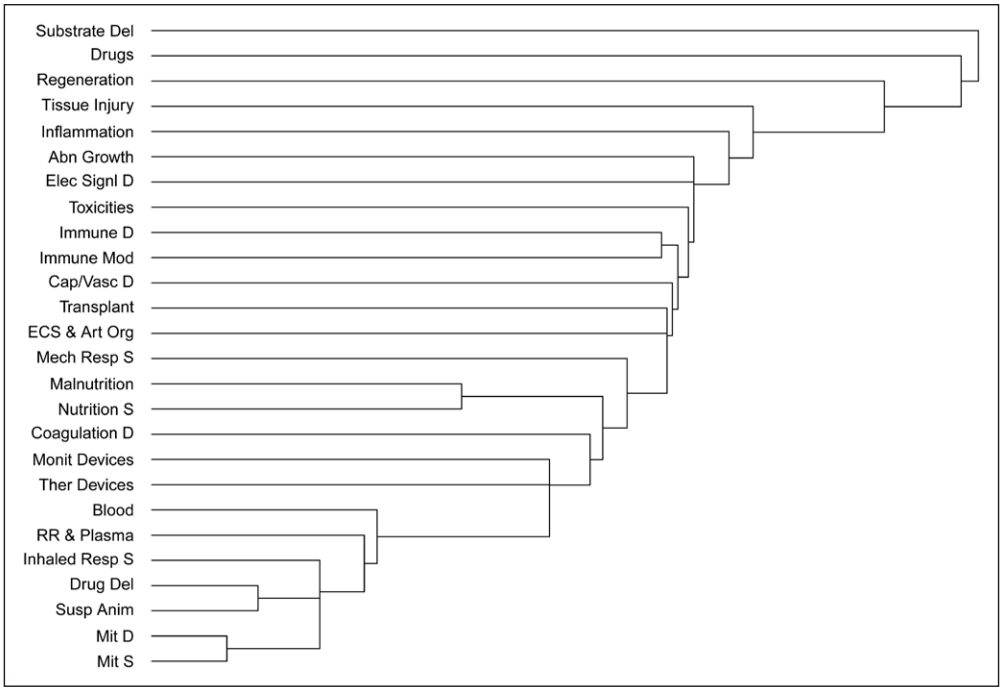

Figure 1. Clustering of pathophysiologies and therapeutic innovations. In this figure, the algorithm recursively combines the pathophysiologies into clusters. The clustering process is seen from bottom to top, with the height of each "branch" reflecting relative similarities between clusters using the Euclidean distance. Longer "branches" indicate weaker associations. Abn Growth = abnormal growth/abnormal cell cycle, blood = blood and blood products, Cap/Vasc D = capillary/vascular dysfunction, coagulation D = coagulation dysfunction, ECS & Art Org = extracorporeal support and artificial organs, Elec Sign D = electrical signaling dysfunction, immune D = immune dysfunction, immune Mod = immune and inflammatory modulation, inhaled Resp S = inhaled respiratory support, Mech Resp S = mechanical respiratory support, Mit D = mitochondrial dysfunction, Mit S = mitochondrial support, Monit Devices = monitoring devices, nutrition = nutritional support, regeneration = cell regeneration, RR & plasma = renal replacement and plasmapheresis, Substrate Del = impaired substrate delivery, Susp Anim = suspended animation, Ther Devices = therapeutic devices, transplant = organ transplant.

DISCUSSION

CPCCRN, first formed in 2005, was funded "to initiate a multicentered program designed to investigate the safety and efficacy of treatment and management strategies to care for critically ill children, as well as the pathophysiologic basis of critical illness and injury in childhood." (34–36) Although the network has placed a high priority on better understanding the pathophysiologies responsible for new morbidities and mortality and the therapeutic advances that might have ameliorated or prevented these adverse outcomes, it had not undertaken a formal assessment of these issues. The primary goal of this initiative was to identify research areas that could have the greatest impact on outcomes.

The major finding of this analysis is the lack of a single dominant pathophysiology or cluster of pathophysiologies responsible for the adverse outcomes. Impaired substrate delivery was the only pathophysiology noted in over half of the individuals (54.1%) and inflammation was the only other pathophysiology noted in over a third of individuals (35.6%). There were no strong pathophysiological associations when assessed with correlation or cluster analyses. Although not a pathophysiology, chronic conditions such as congenital heart disease, neuromuscular conditions, or malignancy were noted as a significant contributor in 53.4% of the cases and were most frequently paired with impaired substrate delivery. Several of the pathophysiological contributors to poor outcomes are potentially approachable without major new advances. Reviewers judged that malnutrition was a significant pathophysiology in 12.3% and toxicities were a significant contributor in 17.5% of cases. These problems can often be approached with emphasis on nutritional support and drug and electrolyte monitoring.

The most common therapeutic advances involved new drugs (51.0%), cell regeneration (39.4%), and inflammatory and immune modulation (27.1%). Proposed therapeutic advances often illustrated the difficulties of caring for patients without effective therapies including cell regeneration (39.4%), improved organ transplant (16.1%), improved extracorporeal support and artificial organs (16.1%), and improved drugs (51.0%). The reviewers often noted the frustrating situation of not having effective therapies available. Although some of these therapies may seem like fantasies, there is sufficient effort to generate optimism that these approaches may improve therapeutic options in the future (37–43).

This effort focusing on the assessment of pathophysiologies and therapeutic needs at the individual patient level is unique, especially for identifying a research agenda. Previous efforts at agenda setting have relied on expert opinion without explicit assessments of the magnitude of the need (11–13). Others, predominantly trauma programs, have focused on preventable acute care deaths identified by routine clinical and review criteria (44, 45). The Pediatric Emergency Care Applied Research Network developed its research priorities using expert opinion that explicitly included prevalence, seriousness, and practicality (46).

There are several important limitations to this study. First, the focus on individual patients required subjective conclusions by experienced content experts conducting the chart reviews and collaboration with central reviewers to insure classification consistency among the sites. Although we provided an organization for the classifications, the classifications at the individual patient level were a subjective interpretation of the medical record. Although previous analysis demonstrated strong inter-rater reliability at two sites (14), this was not done at all sites. Second, the classification schemes for

both pathophysiologies and therapeutic advances are unique. It remains to be seen how useful these classifications will be. Third, this article does not focus on prevention or the timing of detection or therapy. The companion analysis includes these issues identified at the patient level (15).

CONCLUSIONS

The research agenda for pediatric critical care should be driven in large part by what is needed to reduce or prevent adverse outcomes. Unfortunately, there was a lack of a dominant causative pathophysiology or needed therapy addition or advance. This diversity makes this task harder. A companion paper analyzes the issue at the patient level, describing the specific issues identified for each of the patients in this analysis (15).

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REFERENCES

1. Centers for Disease Control: ICD-10-CM Official Guidelines for Coding and Reporting FY 2019 (October 1, 2018 - September 30, 2019). 2019. Available at: https://www.cdc.gov/nchs/icd/data/10cmguidelines-FY2019-final.pdf. Accessed December 27, 2018
2. Bone MF, Feinglass JM, Goodman DM: Risk factors for acquiring functional and cognitive disabilities during admission to a PICU*. *Pediatr Crit Care Med* 2014; 15:640–648
3. Watson RS, Choong K, Colville G, et al: Life after critical illness in children-toward an understanding of pediatric post-intensive care syndrome. *J Pediatr* 2018; 198:16–24
4. Jones S, Rantell K, Stevens K, et al; United Kingdom Pediatric Intensive Care Outcome Study Group: Outcome at 6 months after admission for pediatric intensive care: A report of a national study of pediatric intensive care units in the United Kingdom. *Pediatrics* 2006; 118:2101–2108
5. Ong C, Lee JH, Leow MK, et al: Functional outcomes and physical impairments in pediatric critical care survivors: A scoping review. *Pediatr Crit Care Med* 2016; 17:e247–e259
6. El-Haddad H, Jang H, Chen W, et al: Effect of ARDS severity and etiology on short-term outcomes. *Respir Care* 2017; 62:1178–1185
7. Carcillo JA, Podd B, Aneja R, et al: Pathophysiology of pediatric multiple organ dysfunction syndrome. *Pediatr Crit Care Med* 2017; 18:S32–S45
8. Seymour CW, Gomez H, Chang CH, et al: Precision medicine for all? Challenges and opportunities for a precision medicine approach to critical illness. *Crit Care* 2017; 21:257
9. Simpson E, Goyal NK, Dhepyasuwan N, et al: Prioritizing a research agenda: A Delphi study of the better outcomes through research for newborns (BORN) network. *Hosp Pediatr* 2014; 4:195–202
10. Collins FS: Research agenda. Opportunities for research and NIH. *Science* 2010; 327:36–37
11. Peters MJ, Argent A, Festa M, et al: The intensive care medicine clinical research agenda in paediatrics. *Intensive Care Med* 2017; 43:1210–1224
12. Deutschman CS, Ahrens T, Cairns CB, et al; Critical Care Societies CollaborativeUSCIITG Task Force on Critical Care Research: Multisociety Task Force for Critical Care Research: Key issues and recommendations. *Crit Care Med* 2012; 40:254–260
13. Weiss CH, Krishnan JA, Au DH, et al; ATS Ad Hoc Committee on Implementation Science: An Official American Thoracic Society Research Statement: Implementation science in pulmonary, critical care, and sleep medicine. *Am J Respir Crit Care Med* 2016; 194:1015–1025
14. Siems A, Banks R, Holubkov R, et al: Structured chart review: Assessment of a structured chart review methodology. *Hosp Pediatr* 2019; 10:61–69
15. Meert KL, Banks R, Holubkov R, et al: Morbidity and mortality in critically ill children. II. Specific diseases, conditions and potential solutions. *Crit Care Med* 2020, in press
16. Pollack MM, Holubkov R, Funai T, et al; *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network: Simultaneous prediction of new morbidity, mortality, and survival without new morbidity from pediatric intensive care: A new paradigm for outcomes assessment. *Crit Care Med* 2015; 43:1699–1709

17. Pollack MM, Holubkov R, Glass P, et al; *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network: Functional Status Scale: New pediatric outcome measure. *Pediatrics* 2009; 124:e18–e28
18. Pollack MM, Holubkov R, Funai T, et al; *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network: Pediatric intensive care outcomes: Development of new morbidities during pediatric critical care. *Pediatr Crit Care Med* 2014; 15:821–827
19. Pollack MM, Holubkov R, Funai T, et al; *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network: The Pediatric Risk of Mortality score: Update 2015. *Pediatr Crit Care Med* 2016; 17:2–9
20. Brennan TA, Leape LL, Laird NM, et al: Incidence of adverse events and negligence in hospitalized patients. Results of the Harvard Medical Practice Study I. *N Engl J Med* 1991; 324:370–376
21. Leape LL, Brennan TA, Laird N, et al: The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II. *N Engl J Med* 1991; 324:377–384
22. Hiatt HH, Barnes BA, Brennan TA, et al: A study of medical injury and medical malpractice. *N Engl J Med* 1989; 321:480–484
23. Vincent JL, Opal SM, Marshall JC, et al: Sepsis definitions: Time for change. *Lancet* 2013; 381:774–775
24. Howell AM, Panesar SS, Burns EM, et al: Reducing the burden of surgical harm: A systematic review of the interventions used to reduce adverse events in surgery. *Ann Surg* 2014; 259:630–641
25. Devlin JW, Mallow-Corbett S, Riker RR: Adverse drug events associated with the use of analgesics, sedatives, and antipsychotics in the intensive care unit. *Crit Care Med* 2010; 38:S231–S243
26. Weiss W, Bolton P: Training in Qualitative Resarch Methods for PVOs and NGOs (and Counterparts). A Trainers Guide to Strenghten Program Planning and Evaluation. January 2000 Edition. Johns Hopkins University, Center for Refugee and Disaster Studies. Baltimore, MD, The Johns Hopkins Univeristy School of Public Health, 2000, pp 1–18
27. Rollins N, Chanza H, Chimbwandira F, et al: Prioritizing the PMTCT implementation research agenda in 3 African countries: INtegrating and Scaling up PMTCT through Implementation REsearch (INSPIRE). *J Acquir Immune Defic Syndr (1999)* 2014; 67(Suppl 2):S108–S113
28. Regis T, Steiner MJ, Ford CA, et al: Professionalism expectations seen through the eyes of resident physicians and patient families. *Pediatrics* 2011; 127:317–324
29. Dosa NP, Boeing NM, Ms N, et al: Excess risk of severe acute illness in children with chronic health conditions. *Pediatrics* 2001; 107:499–504
30. R-Core-Team: R: A Language and Environment for Statistical Computing, 2018. Available at: https://www.R-project.org/. Accessed April 1, 2019
31. Lance GN, Williams W: Mixed-data classificatory programs I.) Agglomerative Systems. *Aust Comput J* 1967; 1:15–20
32. Wickham H: Reshaping data with the reshape package. *J Stat Softw* 2007; 21:1–20
33. Wickham H: ggplot2: Elegant Graphics for Data Analysis. New York, NY, Springer-Verlag, 2016
34. Department of Health and Human Services (DHHS): Collaborative Pediatric Critical Care Research Network. 2004. Available at: https://www.grants.nih.gov/grants/guide/rfa-files/RFA-HD-04-004.html. Accessed December 27, 2018
35. Willson DF, Dean JM, Meert KL, et al; *Eunice Kennedy Shriver* National Institute of Child Health, and Human Development Collaborative Pediatric Critical Care Research Network: Collaborative Pediatric Critical Care Research Network: Looking back and moving forward. *Pediatr Crit Care Med* 2010; 11:1–6
36. Willson DF, Dean JM, Newth C, et al: Collaborative Pediatric Critical Care Research Network (CPCCRN). *Pediatr Crit Care Med* 2006; 7:301–307
37. Sueblinvong V, Weiss DJ: Cell therapy approaches for lung diseases: Current status. *Curr Opin Pharmacol* 2009; 9:268–273
38. Werner JK, Stevens RD: Traumatic brain injury: Recent advances in plasticity and regeneration. *Curr Opin Neurol* 2015; 28:565–573
39. Möbius MA, Thébaud B: Stem cells and their mediators - next generation therapy for bronchopulmonary dysplasia. *Front Med (Lausanne)* 2015; 2:50
40. Jiang L, Jones S, Jia X: Stem cell transplantation for peripheral nerve regeneration: Current options and opportunities. *Int J M Sci* 2017; 18:94
41. Thorgersen EB, Barratt-Due A, Haugaa H, et al: The role of complement in liver injury, regeneration, and transplantation. *Hepatology* 2019; 70:725–736
42. Ciccocioppo R, Dos Santos CC, Baumgart DC, et al: Proceedings of the signature series event of the international society for cellular therapy: "Advancements in cellular therapies and regenerative medicine in digestive diseases," London, United Kingdom, May 3, 2017. *Cytotherapy* 2018; 20:461–476
43. Oh DK, Kim YS, Oh YM: Lung regeneration therapy for chronic obstructive pulmonary disease. *Tuberc Respir Dis (Seoul)* 2017; 80:1–10
44. Jenkins DH, Cioffi WG, Cocanour CS, et al; Coalition for National Trauma Research (CNTR): Position statement of the Coalition for National Trauma Research on the National Academies of Sciences, Engineering and Medicine report, A National Trauma Care System: Integrating Military and Civilian Trauma Systems to Achieve Zero Preventable Deaths After Injury. *J Trauma Acute Care Surg* 2016; 81:816–818
45. Berwick DM, Downey AS, Cornett EA: A national trauma care system to achieve zero preventable deaths after injury: Recommendations from a National Academies of Sciences, Engineering, and Medicine Report. *JAMA* 2016; 316:927–928
46. Tzimenatos L, Kim E, Kuppermann N: The Pediatric Emergency Care Applied Research Network: A history of multicenter collaboration in the United States. *Pediatr Emerg Care* 2015; 31:70–76