Morbidity and Mortality in Critically Ill Children. II. A Qualitative Patient-Level Analysis of Pathophysiologies and Potential Therapeutic Solutions*

Kathleen L. Meert MD[1]; Russell Banks, MS[2]; Richard Holubkov, PhD[2]; Murray M. Pollack, MD[3]; and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network

Objectives: To describe at the individual patient level the pathophysiologic processes contributing to morbidity and mortality in PICUs and therapeutic additions and advances that could potentially prevent or reduce morbidity and mortality.

Design: Qualitative content analysis of intensivists' conclusions on pathophysiologic processes and needed therapeutic advances formulated by structured medical record review.

Setting: Eight children's hospitals affiliated with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network.

Patients: A randomly selected cohort of critically ill children with a new functional morbidity or mortality at hospital discharge. New morbidity was assessed using the Functional Status Scale and defined as worsening by two or more points in a single domain from preillness baseline.

Interventions: None.

Measurements and Main Results: Of 292 children, 175 (59.9%) had a new morbidity and 117 (40.1%) died. The most common pathophysiology was impaired substrate delivery ($n = 158$, 54.1%) manifesting as global or regional hypoxia or ischemia due to low cardiac output or cardiac arrest. Other frequent pathophysiologies were inflammation ($n = 104$, 35.6%) related to sepsis, respiratory failure, acute respiratory distress syndrome, or multiple organ dysfunction; and direct tissue injury ($n = 64$, 21.9%) including brain and spinal cord trauma. Chronic conditions were often noted ($n = 156$, 53.4%) as contributing to adverse outcomes. Drug therapies ($n = 149$, 51.0%) including chemotherapy, inotropes, vasoactive agents, and sedatives were the most frequently proposed needed therapeutic advances. Other frequently proposed therapies included cell regeneration ($n = 115$, 39.4%) mainly for treatment of neuronal injury, and improved immune and inflammatory modulation ($n = 79$, 27.1%).

Conclusions: Low cardiac output and cardiac arrest, inflammation-related organ failures, and CNS trauma were the most common pathophysiologies leading to morbidity and mortality in PICUs. A research agenda focused on better understanding and treatment of these conditions may have high potential to directly impact patient outcomes. (*Crit Care Med* 2020; 48:799–807)

Key Words: child; infant; morbidity; mortality; pediatric intensive care unit; research agenda

*See also p. 921.

[1]Department of Pediatrics, Children's Hospital of Michigan, Wayne State

[2]Department of Pediatrics, University of Utah School of Medicine, Salt Lake City, UT.

[3]Department of Pediatrics, Children's National Health System and the George Washington University School of Medicine and Health Sciences, Washington, DC.

DOI: 10.1097/CCM.0000000000004332

In 2005, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development established the Collaborative Pediatric Critical Care Research Network (CPCCRN) (1). The purpose of the CPCCRN was 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 (1, 2). The CPCCRN seeks to reduce morbidity and mortality in pediatric critical illness and injury and provide a framework for developing the scientific basis of pediatric critical care practice (3). Since its inception, the CPCCRN has accomplished numerous research studies covering a broad range of topics (3–5). However, to fulfill the CPCCRN's intended purpose, a research agenda is needed with the explicit objectives of reducing morbidity and mortality in pediatric intensive care by addressing underlying pathophysiologies and developing new therapeutic options. Interventional trials to identify evidence-based best practices are needed in pediatric intensive

care (6–9). Interventional trials that evaluate therapies directed at the pathophysiologic processes most often leading to morbidity and mortality in PICUs have potential to improve outcomes for the greatest number of critically ill children. Thus, identifying these pathophysiologies and needed therapies is an essential first step in developing impactful interventional trials.

The Informing the Research Agenda for PICUs (IRA) study was conducted by the CPCCRN to determine 1) the important pathophysiologic processes resulting in morbidity and mortality and 2) the needed therapeutic additions and advances, including life support methods, that could potentially prevent or reduce morbidity and mortality (10, 11). The IRA study categorized pathophysiologies associated with morbidity or mortality, assessed their frequencies and associations, and described potential therapeutic advances to address these pathophysiologies through structured medical record reviews (11). The objective of this report is to describe at the individual patient level the details of the pathophysiologic processes and needed therapeutic advances previously identified in the IRA study. By "unpacking" the content previously categorized under each broad pathophysiology or potential therapy, greater insight into the components of a research agenda intended to reduce morbidity and mortality from pediatric critical illness or injury can be gained.

MATERIALS AND METHODS

Design and Setting

The IRA study was a structured medical record review conducted across eight children's hospitals affiliated with the CPCCRN (11). The central Institutional Review Board for the CPCCRN approved the study.

Participants

Children in the IRA study originated from the Trichotomous Outcome Prediction in Critical Care (TOPICC) study conducted by the CPCCRN between December 4, 2011, and April 7, 2013 (12). Children recruited to TOPICC with a significant new morbidity or mortality at hospital discharge were eligible for the IRA study. A new morbidity was determined using the Functional Status Scale (FSS) (13). FSS assesses function in six domains including mental, sensory, communication, motor, feeding, and respiratory. Domain scores range from one (normal) to five (very severe dysfunction), and total scores range from six to 30. A new morbidity was defined as an increase in the FSS score of two or more in a single domain from the child's preillness baseline. Mortalities were included if their admission risk of mortality was less than 80% (14). Of 10,078 children recruited to the TOPICC study, 681 had a significant new morbidity or mortality at hospital discharge and were eligible for the IRA study. Eligible children were centrally randomized by site and the randomization list and core study data were provided to the sites. Site investigators reviewed the medical records of eligible children in the randomization sequence until 25 or more children per site were included. Across all sites, the medical records of 327 children were evaluated. Because this is a descriptive study, no formal power analysis was conducted. The demographics, baseline clinical characteristics, and outcomes were not significantly different between the 327 children evaluated and those not evaluated (**Supplemental Digital Content 1**, http://links.lww.com/CCM/F414). Among the 327 children evaluated, a new morbidity or mortality was not confirmed in 35 children, resulting in a final cohort of 292 children.

Procedures

The structured medical record review methodology has been previously described (10, 11). Briefly, site reviewers (third year pediatric critical care fellows or attending intensivists) first confirmed each child's core study data including hospital and PICU admission and discharge dates, baseline and hospital discharge FSS total and domain scores, and mortality. FSS scores in the TOPICC dataset were obtained using information from bedside caregivers as well as the medical record. When FSS scores could not be confirmed using the medical record alone, the child was excluded.

Pathophysiologic processes assessed as contributory to the child's new morbidity or mortality, and the therapeutic advances that could have reduced the morbidity or prevented the mortality were selected from predefined lists (10, 11). In addition, the site reviewer described the processes or advances using a free text format, including the pathophysiologic sequence leading to morbidity or mortality. Site reviewers discussed each case with a central reviewer (K.L.M., M.M.P.) to ensure consistency in the classifications.

Data Analysis

The descriptive text for each pathophysiologic process or needed therapeutic advance was excerpted. The two central reviewers conducted a qualitative content analysis on the descriptive text using a conventional approach to develop subcategories of pathophysiologies and therapies (15). Qualitative content analysis is a method of examining textual data for the purpose of classifying large amounts of text into an efficient number of categories that represent similar meanings (15). In conventional content analysis, the categories are derived from the data during the analysis. First, the two central reviewers read all the descriptive text provided for each pathophysiologic process and therapeutic advance to develop subcategories that identified the specific issues relevant to each pathophysiologic or therapeutic category. Next, for each case, the reviewers classified the pathophysiologic processes or therapeutic advances into one or more subcategories. Last, the number of cases in each category and subcategory were counted. Categories and subcategories with descriptive details are presented in decreasing order of frequency (**Supplemental Digital Content 2**, http://links.lww.com/CCM/F415).

RESULTS

Of the 292 children included in the study, median age was 2.4 years (interquartile range, 0.4–9.5 yr); 162 (55.5%) were male and 135 (46.2%) were White. One-hundred seventy-five children (59.9%) had a new morbidity and 117 died (40.1%).

Pathophysiologic Processes

Impaired substrate delivery (n = 158, 54.1%) was the most frequent pathophysiologic process identified (**eTable 1**, Supplemental Digital Content 2, http://links.lww.com/CCM/F415). Subcategories included ischemia (27%), hypoxia (16%), or both (57%) and were characterized as occurring either globally (88%) or regionally (12%). Global disorders of hypoxia or ischemia were most often due to low cardiac output or cardiac arrest. Regional disorders were due to decreased cerebral perfusion (**Table 1**).

Inflammation (n = 104, 35.6%) was subcategorized as infection-related (78%) or non-infection related (28%) with several children having both types of inflammation (eTable 2, Supplemental Digital Content 2, http://links.lww.com/CCM/F415). Infection-related inflammation most often manifested as sepsis, respiratory failure with or without acute respiratory distress syndrome (ARDS), and multiple organ dysfunction syndrome (MODS). The most common infectious agents identified were viral or an unspecified organism. The most frequent noninfectious inflammatory process was cardiopulmonary bypass-related reperfusion injury.

Direct tissue injury (n = 64, 21.9%) was most often subcategorized as trauma (58%) or surgical/device related-injury (17%) (eTable 3, Supplemental Digital Content 2, http://links.lww.com/CCM/F415). Trauma was further characterized by intent including accidental, nonaccidental, or unknown. Regardless of intent, most cases of trauma involved either a brain or spinal cord injury (86%).

Electrical signaling dysfunction (n = 52, 17.8%) included neurologic (69%), cardiac (29%), or both (2%) conditions (eTable 4, Supplemental Digital Content 2, http://links.lww.com/CCM/F415). Neurologic conditions were mostly seizure disorders, and cardiac conditions were dysrhythmias.

Abnormal growth/abnormal cell cycle (n = 52, 17.8%) included malignancies (63%) and major congenital malformations (37%) (eTable 5, Supplemental Digital Content 2, http://links.lww.com/CCM/F415). Malignancies contributing to morbidity or mortality were primarily leukemias. Congenital malformations were mostly cardiac.

Capillary/vascular dysfunction (n = 52, 17.8%) was most often subcategorized as anasarca related to sepsis/MODS/ARDS or due to cardiac failure (eTable 6, Supplemental Digital Content 2, http://links.lww.com/CCM/F415). Other forms of capillary/vascular dysfunction included pulmonary hypertension and cerebral edema.

Toxicities (n = 51, 17.5%) were most often drug related (71%) (eTable 7, Supplemental Digital Content 2, http://links.lww.com/CCM/F415). Sedatives were the most common cause of drug toxicity leading to withdrawal and deconditioning syndrome. Toxic effects of chemotherapy and anticonvulsants were also frequent. Nondrug related toxicities included electrolyte disorders (12%) and toxic effects of endogenous substances (12%) from metabolic disorders or hepatic failure.

Immune dysfunction (n = 49, 16.8%) included subcategories of decreased (41%), increased (20%), both decreased and increased (16%), or otherwise dysregulated (22%) immunity (eTable 8, Supplemental Digital Content 2, http://links.lww.com/CCM/F415). The most frequently described contributors to altered immunity included immune suppressing drugs, malignancies, and bone marrow transplant.

Coagulation dysfunction (n = 39, 13.4%) was subcategorized as bleeding (62%), thrombosis (31%) and both bleeding and thrombosis (8%) (eTable 9, Supplemental Digital Content 2, http://links.lww.com/CCM/F415). Nearly all cases of bleeding and thrombosis were acquired rather than congenital disorders. Common causes of bleeding included disseminated intravascular coagulation, trauma, extracorporeal membrane oxygenation (ECMO), and thrombocytopenia secondary to leukemia. Common causes of thrombosis included infection and ECMO. Site of bleeding or thrombosis most often resulting in morbidity or mortality was intracranial (i.e., hemorrhage or stroke).

TABLE 1. Pathophysiologies Contributing to Morbidity or Mortality in Pediatric Intensive Care

Pathophysiology	n (%)[a]	Supplemental Table With Patient-Level Details
Impaired substrate delivery	n = 158	eTable 1 (Supplemental Digital Content 2, http://links.lww.com/CCM/F415)
Ischemia	43 (27)	
Global	35 (22)	
Regional	8 (5)	
Hypoxia (all global)	25 (16)	
Hypoxia and ischemia	90 (57)	
Global	79 (50)	
Regional	11 (7)	
Inflammation[b]	n = 104	**eTable 2** (Supplemental Digital Content 2, http://links.lww.com/CCM/F415)
Infection-related	81 (78)	
Oxidative injury or other inflammation (noninfectious)	29 (28)	

(*Continued*)

TABLE 1. (*Continued*). Pathophysiologies Contributing to Morbidity or Mortality in Pediatric Intensive Care

Pathophysiology	*n* (%)[a]	Supplemental Table With Patient-Level Details
Tissue injury (direct)	*n* = 64	**eTable 3** (Supplemental Digital Content 2, http://links.lww.com/CCM/F415)
Trauma	37 (58)	
Surgical/device injury	11 (17)	
Ventilator-associated lung injury	7 (11)	
Burns	3 (5)	
Other/unknown	6 (9)	
Electrical signaling dysfunction	*n* = 52	**eTable 4** (Supplemental Digital Content 2, http://links.lww.com/CCM/F415)
Neurologic	36 (69)	
Cardiac	15 (29)	
Neurologic and cardiac	1 (2)	
Abnormal growth/abnormal cell cycle	*n* = 52	**eTable 5** (Supplemental Digital Content 2, http://links.lww.com/CCM/F415)
Malignancy	33 (63)	
Congenital malformation	19 (37)	
Capillary/vascular dysfunction	*n* = 52	**eTable 6** (Supplemental Digital Content 2, http://links.lww.com/CCM/F415)
Toxicities	*n* = 51	**eTable 7** (Supplemental Digital Content 2, http://links.lww.com/CCM/F415)
Drug	36 (71)	
Electrolyte	6 (12)	
Endogenous substance	6 (12)	
Other	3 (6)	
Immune dysfunction	*n* = 49	**eTable 8** (Supplemental Digital Content 2, http://links.lww.com/CCM/F415)
Decreased function	20 (41)	
Increased function	10 (20)	
Decreased and increased function	8 (16)	
Other	11 (22)	
Coagulation dysfunction	*n* = 39	**eTable 9** (Supplemental Digital Content 2, http://links.lww.com/CCM/F415)
Bleeding (acquired)	24 (62)	
Thrombosis (acquired)	11 (28)	
Bleeding (acquired) and thrombosis (acquired)	3 (8)	
Thrombosis (congenital) and thrombosis (acquired)	1 (3)	
Malnutrition	*n* = 36	**eTable 10** (Supplemental Digital Content 2, http://links.lww.com/CCM/F415)
General malnutrition	35 (97)	
Specific nutrient deficiency (vitamin D deficiency)	1 (3)	
Mitochondrial dysfunction	*n* = 5	**eTable 11** (Supplemental Digital Content 2, http://links.lww.com/CCM/F415)
Other	*n* = 19	**eTable 12** (Supplemental Digital Content 2, http://links.lww.com/CCM/F415)

[a]Percentages refer to the individual pathophysiologic category.
[b]Six subjects had more than one type of inflammation.

Malnutrition (n = 36, 12.3%) was subcategorized as general malnutrition (97%) or specific nutrient deficiency (3%) (eTable 10, Supplemental Digital Content 2, http://links.lww.com/CCM/F415). Malnutrition was also subcategorized by duration (i.e., acute, chronic, acute on chronic). Most cases were acute on chronic (47%); of these, most were due to congenital heart disease or malignancy with a complication preventing adequate nutritional intake.

Mitochondrial dysfunction (n = 5, 1.7%) included congenital myopathies/metabolic disorders, and lactic acidosis associated with MODS (eTable 11, Supplemental Digital Content 2, http://links.lww.com/CCM/F415).

Pathophysiologic processes categorized as other (n = 19, 6%) included deconditioning syndrome, acute renal failure, psychiatric disorder, and genetic metabolic disease (eTable 12, Supplemental Digital Content 2, http://links.lww.com/CCM/F415).

Chronic conditions (n = 156, 53.4%) frequently contributed to adverse outcomes (**eTable 13**, Supplemental Digital Content 2, http://links.lww.com/CCM/F415). Congenital heart disease, particularly hypoplastic left heart syndrome, neuromuscular disorders, and malignancies were the most common chronic conditions described.

Needed Therapeutic Advances

Drugs were the most frequently identified therapy in need of advancement (n = 149, 51.0%) (**eTable 14**, Supplemental Digital Content 2, http://links.lww.com/CCM/F415). Drug advancements most frequently described included chemotherapy with greater effectiveness and less side effects (20%), inotropes (17%) and vasoactive agents (16%) for impaired substrate delivery, sedatives (13%) with less propensity for withdrawal and deconditioning syndrome, and antiviral agents (13%) (**Table 2**). Other needed drug advancements included improved anticonvulsants (11%), antibiotics (10%), and anticoagulation agents (7%). Pulmonary vasodilators were a specific type of vasoactive agent identified.

TABLE 2. Therapeutic Advances for All Categories and Subcategories With Atleast 10 Cases

Therapy	*n* (%)	Supplemental Table With Patient-Level Details
Drugs[a]	*n* = 149	eTable 14 (Supplemental Digital Content 2, http://links.lww.com/CCM/F415)
Chemotherapy	30 (20)	
Inotropes	26 (17)	
Vasoactive agents	24 (16)	
Sedatives	20 (13)	
Antiviral	20 (13)	
Anticonvulsants	17 (11)	
Antibacterial	15 (10)	
Anticoagulation	10 (7)	
Cell regeneration	*n* = 115	**eTable 15** (Supplemental Digital Content 2, http://links.lww.com/CCM/F415)
Neuronal	80 (70)	
Cardiovascular	13 (11)	
Immune and inflammatory modulation	*n* = 79	**eTable 16** (Supplemental Digital Content 2, http://links.lww.com/CCM/F415)
Immune suppression only	32 (41)	
Immune suppression and enhancement	13 (16)	
Other/unspecified	25 (32)	
Extracorporeal support and artificial organs	*n* = 47	**eTable 17** (Supplemental Digital Content 2, http://links.lww.com/CCM/F415)
Extracorporeal circulatory support only	29 (62)	
Extracorporeal circulatory support and oxygenation	11 (23)	
Organ transplant	*n* = 47	**eTable 18** (Supplemental Digital Content 2, http://links.lww.com/CCM/F415)
Heart	25 (53)	
Mechanical respiratory support	*n* = 41	**eTable 19** (Supplemental Digital Content 2, http://links.lww.com/CCM/F415)

(*Continued*)

TABLE 2. (*Continued*). Therapeutic Advances for All Categories and Subcategories With Atleast 10 Cases

Therapy	*n* (%)	Supplemental Table With Patient-Level Details
Nutritional support	*n* = 39	**eTable 20** (Supplemental Digital Content 2, http://links.lww.com/CCM/F415)
Better tolerated enteral formulas[b]	10 (26)	
Therapeutic devices	*n* = 28	**eTable 21** (Supplemental Digital Content 2, http://links.lww.com/CCM/F415)
Monitoring devices	*n* = 28	**eTable 22** (Supplemental Digital Content 2, http://links.lww.com/CCM/F415)
Blood and blood products	*n* = 9	**eTable 23** (Supplemental Digital Content 2, http://links.lww.com/CCM/F415)
Renal replacement and plasmapheresis	*n* = 8	**eTable 24** (Supplemental Digital Content 2, http://links.lww.com/CCM/F415)
Mitochondrial support	*n* = 6	**eTable 25** (Supplemental Digital Content 2, http://links.lww.com/CCM/F415)
Inhaled respiratory support	*n* = 5	**eTable 26** (Supplemental Digital Content 2, http://links.lww.com/CCM/F415)
Suspended animation	*n* = 2	**eTable 27** (Supplemental Digital Content 2, http://links.lww.com/CCM/F415)
Other	*n* = 92	**eTable 28** (Supplemental Digital Content 2, http://links.lww.com/CCM/F415)
Treatment for hypoxic-ischemic encephalopathy	14 (15)	
Trauma prevention	12 (13)	
Gene therapy	11 (12)	
Better surgery for congenital heart disease (non-hypoplastic left heart syndrome)	10 (11)	

[a]Subjects can be in need of more than one type of drug advance or addition.
[b]Better tolerated enteral formulas include tolerating high-calorie formulas and tolerating enteral formula in face of various conditions such as graft-versus-host disease of gut or Crohn's disease.

Cell regeneration (*n* = 115, 39.4%) was also frequently identified as a needed therapy (eTable 15, Supplemental Digital Content 2, http://links.lww.com/CCM/F415). Neuronal regeneration (70%) for treatment of traumatic brain and spinal cord injury and hypoxic-ischemic encephalopathy was the most common type of cell regeneration identified, followed by cardiovascular regeneration (11%) for congenital heart defects.

Advances in immune and inflammatory modulation (*n* = 79, 27.1%) included improved therapies for immune suppression (41%), immune enhancement (11%), or both (16%) (eTable 16, Supplemental Digital Content 2, http://links.lww.com/CCM/F415). These therapies were needed most often to treat systemic inflammatory response syndrome, CNS inflammation, lung inflammation with or without ARDS, infection, transplant rejection, and graft-versus-host disease (GVHD).

Advances in extracorporeal support and artificial organs (*n*=47,16.1%) were needed primarily to support circulation (62%), oxygenation (11%), or both (23%) (eTable 17, Supplemental Digital Content 2, http://links.lww.com/CCM/F415). Some needed improvements in extracorporeal support included faster and more accessible support; support with greater potential for long-term use as a bridge to transplant or recovery; improved anticoagulation; less inflammatory activation; and less invasive techniques.

Organ transplant advancements (*n* = 47, 16.1%) were needed for heart, bone marrow, lung, liver, small bowel, and multiple organ transplants (eTable 18, Supplemental Digital Content 2, http://links.lww.com/CCM/F415). Needed improvements included ability to provide earlier organ transplant, increased organ availability, better evaluation criteria for recipient listing, and prevention and treatment of transplant-related complications including rejection, GVHD, and post-transplant lymphoproliferative disorder.

Mechanical respiratory support advancements (*n* = 41, 14.0%) were needed for several disorders including ARDS and pulmonary hypertension (eTable 19, Supplemental Digital Content 2, http://links.lww.com/CCM/F415). Needed improvements included reduced potential for ventilator-induced lung injury, better noninvasive ventilation, ventilation that requires less sedation, and better home and negative-pressure ventilators.

Advances in nutritional support (*n* = 39, 13.4%) included enteral formulas better tolerated in specific conditions and improved nutritional monitoring (eTable 20, Supplemental Digital Content 2, http://links.lww.com/CCM/F415). Improved

monitoring included energy expenditure, nutritional immunity, and home monitoring of nutritional intake.

Advances in therapeutic devices (n = 28, 9.6%) included increased availability of pediatric sizes, less thrombogenic materials, less invasive, improved durability, and greater resistance to infection (eTable 21, Supplemental Digital Content 2, http://links.lww.com/CCM/F415).

Advances in monitoring devices (n = 28, 9.6%) included better ability to continuously monitor cardiac output and regional blood flow and brain oxygenation (eTable 22, Supplemental Digital Content 2, http://links.lww.com/CCM/F415).

Blood and blood product advancements (n = 9, 3.1%) included better products to treat coagulopathy, hemorrhagic shock, and local bleeding, as well as advances to allow granulocyte transfusions with less side effects (eTable 23, Supplemental Digital Content 2, http://links.lww.com/CCM/F415).

Advances in renal replacement and plasmapheresis (n = 8, 2.7%) included improved fluid removal during low cardiac output states, renal replacement therapy using peripheral vascular access, and improved knowledge about drug pharmacokinetics (eTable 24, Supplemental Digital Content 2, http://links.lww.com/CCM/F415).

Advances in mitochondrial support (n = 6, 2.1%) were needed for genetic mitochondrial disorders and mitochondrial dysfunction associated with sepsis, MODS, and cardiopulmonary bypass (eTable 25, Supplemental Digital Content 2, http://links.lww.com/CCM/F415).

Advances in inhaled respiratory support (n = 5, 1.7%) included therapies for pulmonary hypertension (eTable 26, Supplemental Digital Content 2, http://links.lww.com/CCM/F415).

Suspended animation (n = 2, 0.7%) was proposed as a technique to provide time to prevent cardiac arrest or mismatch between cellular energy supply and demand during cardiac arrest (eTable 27, Supplemental Digital Content 2, http://links.lww.com/CCM/F415).

Needed therapeutic advances categorized as other (n = 92, 31.5%) included treatment for hypoxic-ischemic encephalopathy, trauma prevention, gene therapy, and better surgeries for congenital heart disease (eTable 28, Supplemental Digital Content 2, http://links.lww.com/CCM/F415).

DISCUSSION

This effort is the first to use in-depth assessments of individual patients from a large multicenter sample to identify the causes of morbidity and mortality in critically ill children and the needed therapeutic advances to reduce these adverse outcomes. Our findings can serve to inform a pediatric intensive care research agenda focused on reducing morbidity and mortality in PICUs. Most research agendas are based on literature review, professional guidelines, conference proceedings, and expert opinion (16–22). Although these sources are important, research agendas based on individual patient data directly driving morbidity and mortality may have greater potential to reduce these adverse outcomes.

Our findings do not comprise a research agenda in themselves but are intended to inform a research agenda for pediatric intensive care. Research agendas may consider many other factors such as the views of patients, families and other stakeholders, the region or country in which the agenda will be applied, methodological practicalities, and ethical implications. Research agendas for intensive care may also evaluate processes other than pathophysiology such as healthcare communication or care delivery, or be directed at outcomes other than morbidity and mortality at hospital discharge (e.g., patient and family satisfaction, long-term outcomes, and reduction in suffering at the end of life). Nevertheless, identification of pathophysiologies and therapeutic deficiencies leading to hospital morbidity and mortality is essential to a research agenda intended to reduce these outcomes.

Impaired substrate delivery, inflammation, and direct tissue injury were the three most frequent pathophysiologic processes in our study. Hypoxia and ischemia due to low cardiac output or cardiac arrest; inflammation related to sepsis, respiratory failure, ARDS, and MODS; and traumatic brain and spinal cord injury were common manifestations of these processes. These pathophysiologies are consistent with research agendas for pediatric intensive care proposed by others (16, 23–25) and with recent topics of CPCCRN research (5, 26–28).

Although not a specific pathophysiology, chronic illness was identified as contributing to morbidity and mortality in over half of cases. Children with chronic illness have been defined in the literature as those who have a chronic physical, developmental, behavioral, or emotional condition and who also require health services beyond that usually required of children (29). The success of research translated into clinical care by disciplines such as neonatology, hematology-oncology, and cardiac surgery have contributed to the increase in children surviving critical illness but with the burden of chronic conditions (30, 31). Children with chronic conditions have been shown to have increasing inpatient resource use, as well as disproportionate use of intensive care services (32, 33). Furthermore, chronic critical illness has recently been defined based on PICU length of stay, frequency of admissions, technology dependence, and persistence of multiple vital organ dysfunction (34). Higher mortality rates have been described for children with chronic critical illness (34). In our study, a definition of chronic illness was not provided to the reviewers. Reviewers were asked to assess, based on data from the medical record, whether a chronic condition contributed to the child's morbidity or mortality in PICU, and to describe the condition. The most common chronic conditions identified were congenital heart disease, neuromuscular disorders, and malignancy. Our findings support the opinions of others advocating for a research agenda aimed at preventing chronic critical illness and improving outcomes when it occurs (34).

The intensivists reviewing medical records in our study suggested a wide variety of needed therapeutic additions and advances. Whereas identification of pathophysiologic processes required intensivists to rely on medical knowledge and experience, proposal of new therapies required hypothetical thinking or "best guesses" as to what might have improved the child's outcome. Advances to drug therapies were most frequently proposed. Reduction in drug toxicity was an important consideration as untoward side effects often contributed to adverse outcomes.

Advances in cell regeneration and immune and inflammatory modulation were also frequently proposed. Neuronal regeneration was described as a treatment for traumatic or hypoxic-ischemic brain injury, and immune and inflammatory modulation as a treatment for CNS inflammation. These findings suggest that new therapies for brain injury should continue as an important component of a pediatric intensive care research agenda.

The strengths of this study include the multicenter design, the structured medical record review that evaluated individual patients, and the reviewers' qualifications and expertise. Additional strengths include the objective definition of a new morbidity based on FSS scores, and the use of qualitative analytic methods to characterize the reviewers' assessments. Limitations include the restriction of participating sites to the CPCCRN, all of which are in the United States; thus, our findings may not be applicable to countries where other diseases are more common or resources less available. Use of predefined categories in the structured medical record review may have constrained reviewers in their selection of pathophysiologies and therapies; however, the category "other" was available and free text descriptions requested for all categories selected. The pathophysiologies and therapies may have been limited by the preexisting concepts, experience, and imagination of the reviewers, yet multiple reviewers were included from multiple sites. Although the intensivists' expertise in pathophysiology was a strength, interdisciplinary input would likely have broadened our findings especially those concerning potential therapeutic advances for the field. Many of the pathophysiologies and needed therapies will require additional basic science investigation before being addressed in the clinical setting; however, our findings may direct basic science toward clinical needs.

CONCLUSIONS

Using patient-level data, we found low cardiac output and cardiac arrest, inflammation-related organ failures, and CNS trauma were the most common pathophysiologic processes leading to morbidity and mortality in PICUs. Chronic illness contributed to poor outcomes in over half of cases. These findings can be used to inform a research agenda for pediatric intensive care. A research agenda based on patient-level data may have high potential to directly impact patient outcomes.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

Supported, in part, by the following cooperative agreements from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services: U10HD050096, U10HD049981, U10HD049983, U10HD050012, U10HD063108, U10HD063114, UG1HD083171, UG1HD083166, UG1HD083170, and U01HD049934.

Drs. Meert's, Banks's, Holubkov's, Pollack's, Berg's, Bolton's, Dean's, Mourani's, Newth's, and Sapru's institutions received funding from the National Institutes of Health (NIH). Drs. Meert, Banks, Holubkov, Pollack, Berg, Bolton, Carcillo, Dean, McQuillen, Mourani, Newth, Notterman, Priestley, Sapru, and Yates received support for article research from the NIH. Dr. Banks disclosed government work. Dr. Holubkov received funding from Pfizer (Data Safety Monitoring Board [DSMB]), Medimmune (DSMB), Physicians Committee for Responsible Medicine (biostatistical consulting), Revance (DSMB), Armaron Bio (DSMB), and DURECT Corporation (biostatistical consultant). Drs. Carcillo's, McQuillen's, and Yates's institutions received funding from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD). Dr. Newth received funding from Philips Research North America and Hamilton Medical AG. Dr. Notterman received funding from the American Board of Pediatrics and Proximity Focal, and he received support for article research from the Russell Sage Foundation, Princeton University, and the University of Utah. Dr. Priestley's institution received funding from Collaborative Pediatric Critical Care Research Network of the NICHD. The remaining authors have disclosed that they do not have any potential conflicts of interest.

Authors from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network (alphabetical order): Christian Bauerfeld, MD, Department of Pediatrics, Children's Hospital of Michigan, Wayne State University, Detroit, MI; David Beyda, MD, Critical Care Medicine, Phoenix Children's Hospital, and University of Arizona College of Medicine-Phoenix, Phoenix, AZ; Robert A. Berg, MD, Department of Anesthesiology and Critical Care, Children's Hospital of Philadelphia, Philadelphia, PA; Melissa M. Bolton, MBA, Department of Pediatrics, University of Utah School of Medicine, Salt Lake City, UT; Yonca Bulut, MD, Department of Pediatrics, UCLA Mattel Children's Hospital, University of California, Los Angeles, CA; Randall S. Burd, MD, PhD, Division of Trauma and Burn Surgery, Center for Surgical Care, Children's National Medical Center, Washington, DC; Joseph Carcillo, MD, Department of Critical Care Medicine, Children's Hospital of Pittsburgh, Pittsburgh, PA; J. Michael Dean, MD, Department of Pediatrics, University of Utah School of Medicine, Salt Lake City, UT; Eleanor Gradidge, MD, Phoenix Children's Hospital, Phoenix, AZ; Mark W. Hall, MD, Division of Critical Care, Department of Pediatrics, Nationwide Children's Hospital, Columbus, OH, and Center for Clinical and Translational Research, The Research Institute at Nationwide Children's Hospital, Columbus, OH; Peter M. Mourani, MD, Department of Pediatrics, University of Colorado School of Medicine and Children's Hospital of Colorado, Aurora, CO; Christopher J. L. Newth, MD, FRCPC, Department of Anesthesiology and Critical Care Medicine, Children's Hospital Los Angeles, University of Southern California Keck School of Medicine, Los Angeles, CA; Daniel A. Notterman, MD, Department of Molecular Biology, Princeton University, 219 Lewis Thomas Laboratory, Princeton, NJ; Margaret A. Priestley, MD, Department of Anesthesiology and Critical Care, Children's Hospital of Philadelphia, Philadelphia, PA; Ashley Siems, MD, Department of Pediatrics, Children's National Health System and the George Washington University School of Medicine and Health Sciences, Washington, DC; David L. Wessel, MD, Department of Pediatrics, Children's National Medical Center and George Washington University School of Medicine, Washington, DC; and Andrew R. Yates, MD, Department of Pediatrics, Nationwide Children's Hospital, The Ohio State University, Columbus, OH.

For information regarding this article, E-mail: kmeert@med.wayne.edu

REFERENCES

1. Department of Health and Human Services. National Institutes of Health. National Institute of Child Health and Human Development: Collaborative Pediatric Critical Care Research Network. 2004. Available at: https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-04-004.html. Accessed March 31, 2020
2. Willson DF, Dean JM, Newth C, et al: Collaborative Pediatric Critical Care Research Network (CPCCRN). *Pediatr Crit Care Med* 2006; 7:301–307
3. Department of Health and Human Services, National Institutes of Health. National Institute of Child Health and Human Development: Pediatric Trauma and Critical Illness Branch. 2019. Available at: https://www.nichd.nih.gov/about/org/der/branches/ptcib. Accessed March 31, 2020
4. 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
5. Collaborative Pediatric Critical Care Research Network: Publications. 2020. Available at: https://www.cpccrn.org/publications/. Accessed March 31, 2020

6. Tabbutt S, Ravishankar C: Update on randomized clinical trials impacting clinical care in pediatric cardiac intensive care. *Congenit Heart Dis* 2007; 2:104–109
7. Duffett M, Choong K, Hartling L, et al: Randomized controlled trials in pediatric critical care: A scoping review. *Crit Care* 2013; 17:R256
8. Choong K, Duffett M, Cook DJ, et al: The impact of clinical trials conducted by research networks in pediatric critical care. *Pediatr Crit Care Med* 2016; 17:837–844
9. Duffett M, Swinton M, Brouwers M, et al: Advancing randomized controlled trials in pediatric critical care: The perspectives of trialists. *Pediatr Crit Care Med* 2018; 19:e595–e602
10. Siems A, Banks R, Holubkov R, et al: Structured chart review: Assessment of a structured chart review methodology. *Hosp Pediatr* 2020; 10:61–69
11. Pollack MM, Banks R, Holubkov R, et al: Morbidity and mortality in critically ill children. I. Pathophysiologies and potential therapeutic solutions. *Crit Care Med* 2020, in press
12. 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
13. 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
14. 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
15. Hsieh HF, Shannon SE: Three approaches to qualitative content analysis. *Qual Health Res* 2005; 15:1277–1288
16. Peters MJ, Argent A, Festa M, et al: The intensive care medicine clinical research agenda in paediatrics. *Intensive Care Med* 2017; 43:1210–1224
17. Baker JN, Levine DR, Hinds PS, et al: Research priorities in pediatric palliative care. *J Pediatr* 2015; 167:467–70.e3
18. Aslakson RA, Reinke LF, Cox C, et al: Developing a research agenda for integrating palliative care into critical care and pulmonary practice to improve patient and family outcomes. *J Palliat Med* 2017; 20:329–343
19. 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
20. Pezold ML, Pusic AL, Cohen WA, et al: Defining a research agenda for patient-reported outcomes in surgery: Using a Delphi survey of stakeholders. *JAMA Surg* 2016; 151:930–936
21. Foster J, Bautista C, Ellstrom K, et al: Creating a research agenda and setting research priorities for clinical nurse specialists. *Clin Nurse Spec* 2018; 32:21–28
22. Stoner MJ, Mahajan P, Bressan S, et al: Pediatric emergency care research networks: A research agenda. *Acad Emerg Med* 2018; 25:1336–1344
23. Nolan JP, Berg RA, Bernard S, et al: Intensive care medicine research agenda on cardiac arrest. *Intensive Care Med* 2017; 43: 1282–1293
24. Perner A, Gordon AC, Angus DC, et al: The intensive care medicine research agenda on septic shock. *Intensive Care Med* 2017; 43:1294–1305
25. Asehnoune K, Balogh Z, Citerio G, et al: The research agenda for trauma critical care. *Intensive Care Med* 2017; 43:1340–1351
26. Berg RA, Sutton RM, Reeder RW, et al; *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network (CPCCRN) PICqCPR (Pediatric Intensive Care Quality of Cardio-Pulmonary Resuscitation) Investigators: Association between diastolic blood pressure during pediatric in-hospital cardiopulmonary resuscitation and survival. *Circulation* 2018; 137:1784–1795
27. Dalton HJ, Reeder R, Garcia-Filion P, et al; *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network: Factors associated with bleeding and thrombosis in children receiving extracorporeal membrane oxygenation. *Am J Respir Crit Care Med* 2017; 196:762–771
28. Carcillo JA, Berg RA, Wessel DL, et al: Three pediatric sepsis-induced multiple organ failure inflammation phenotypes: A multicenter study. *Crit Care Med* 2019; 47:21
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. Grosfeld JL: William H. Harridge memorial lecture: "Progress and its unintended consequences." *Am J Surg* 2010; 199:284–288
31. Ministeri M, Alonso-Gonzalez R, Swan L, et al: Common long-term complications of adult congenital heart disease: Avoid falling in a H.E.A.P. *Expert Rev Cardiovasc Ther* 2016; 14:445–462
32. Simon TD, Berry J, Feudtner C, et al: Children with complex chronic conditions in inpatient hospital settings in the United States. *Pediatrics* 2010; 126:647–655
33. Chan T, Rodean J, Richardson T, et al: Pediatric critical care resource use by children with medical complexity. *J Pediatr* 2016; 177:197–203.e1
34. Shapiro MC, Henderson CM, Hutton N, et al: Defining pediatric chronic critical illness for clinical care, research, and policy. *Hosp Pediatr* 2017; 7:236–244