NICHD's Collaborative Pediatric Critical Care Research Network (CPCCRN): The First 10 Years

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Background and Introduction

Less than 30 years have passed since pediatric critical care became eligible for board certification as a distinct medical subspecialty. The number of fellows entering subspecialty training in pediatric critical care has increased significantly over the past two decades, as has the number of Pediatric Critical Care Units (PICUs) and the number of PICU beds; at the same time, the number of general pediatric ward beds and total pediatric discharges in the United States has continued to decrease. Known as pediatric intensivists, pediatric critical care physicians care for severely ill children with complex medical needs. Many children admitted to the PICU suffer from conditions affecting multiple organs, and undergo complex treatment plans including multiple medications, machines, and other interventions. Focus in these busy and urgent environments has been more on clinical service than active research. However, the complex and unique environment of the PICU demands an evidence base designed specifically to optimize management of critical pediatric illness.

The Collaborative Pediatric Critical Care Research Network

In April 2005, the National Institutes of Health (NIH) *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) established the Collaborative Pediatric Critical Care Research Network (CPCCRN) to investigate the safety and efficacy of treatment and management strategies to care for critically ill children and to address the pathophysiological bases of critical illness and injury in childhood. The CPCCRN establishes and maintains the national infrastructure required for a network of academic centers to perform clinical trials and descriptive and translational research to help improve care for children who are critically ill.

In the first funding cycle the CPCCRN consisted of six clinical sites, and a Data Coordinating Center (DCC). The CPCCRN underwent competitive renewal in the summer of 2009, and funded seven clinical sites and the DCC. The network underwent a third competitive renewal in 2014 with announcement of the Cycle 3 sites

pending. In FY 2012, the CPCCRN budget was $4.7 million with other grants supporting $2.1 million in protocols that involve CPCCRN sites. The average annual CPCCRN budget for Cycle 2 was $4.85 million per year. The focus of this report is on the first two funding cycles. The CPCCRN was originally housed within the National Center for Medical Rehabilitation Research at NICHD. In 2012, the NICHD's Critical Care Research Program, which includes the CPCCRN, was incorporated into was the newly-established Pediatric Trauma and Critical Illness Branch (PTCIB). CPCCRN is is the only NIH-funded network focused on non-neonatal pediatric critical care and is designed to improve public understanding of a much-needed area of research and clinical service.

As shown in Exhibit 1, the CPCCRN sites have been located at university and children's hospital sites throughout the United States.

Exhibit 1: CPCCRN Sites in the U.S.

For Cycle 1, the six funded CPCCRN sites reported a total of 237 PICU beds with 11,450 annual PICU admissions. As of 2013, the seven sites in Cycle 2 reported 327 PICU beds with 16,900 annual PICU admissions. Exhibit 2 shows site-specific information.

Exhibit 2: CPCCRN Site Information

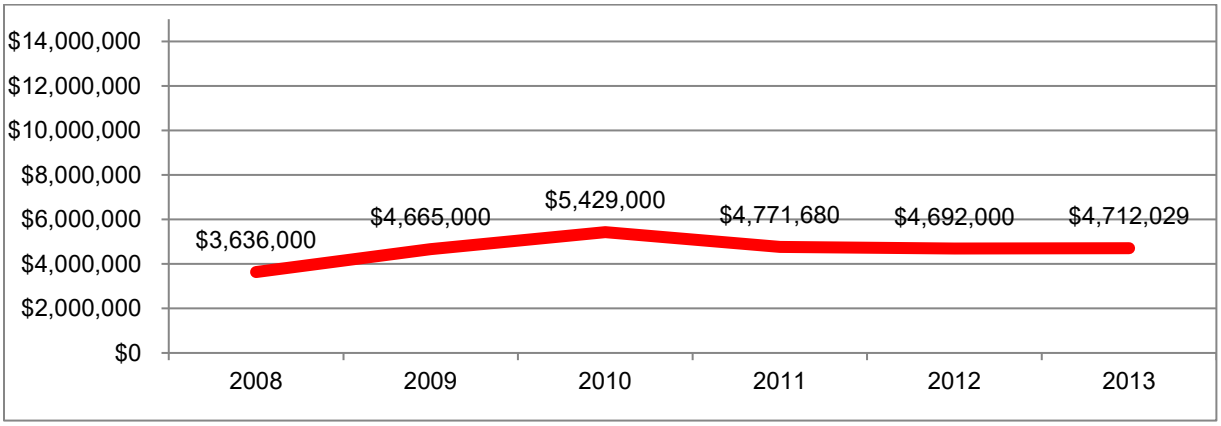
Institution	Acroynm	# Of PICU Beds (2013)	# Of Annual Admissions (2013)	Cycle One 2004-2009	Cycle Two 2010-2014
Children's National Medical Center	CNMC	32	1,400	Yes	Yes
Phoenix Children's Hospital	PHNX	40	2,500	No	Yes
University of Pittsburgh Medical Center	UPMC	50	2,500	Yes	Yes
Children's Hospital Los Angeles-USC/UCLA	CHLA	68	3,100	Yes	Yes
Children's Hospital of Michigan (Wayne State University)	CHOM	30	1,600	Yes	Yes
Arkansas Children's Hospital	ARCH	31	1,350	Yes	No
Seattle Children's Hospital	SEAT	26	1,500	Yes	No
Children's Hospital of Philadelphia	CHOP	77	4,000	No	Yes
University of Michigan Ann Arbor	MICH	30	1,800	No	Yes
University of Utah (DCC)	DCC	--	--	Yes	Yes

Each CPCCRN site supports a Principal Investigator (PI), an Alternate PI/Co-Investigator (Alt-PI), and a Research Coordinator (RC). The budget for each CPCCRN site is set to allow for funding the PI at approximately 20 percent effort, the Alternate PI at 5-10 percent effort, and the Research Coordinator at 100 percent effort; these are guidelines, however, and some centers have chosen

slightly different distributions. The Principal Investigator is required to be a senior pediatric intensivist. The Research Coordinators are typically pediatric critical care nurses with considerable clinical and research experience. The Research Coordinator is responsible for study and protocol implementation. The CPCCRN network has implemented 16 protocols during its history, with 6 studies completed and 10 current. All sites participate in all protocols.

The DCC provides statistical services, research design and protocol development assistance, training, population tracking, and website, reporting, information technology, and logistics services. The DCC provides a central repository for data generated by each of the clinical sites; works with the sites to implement CPCCRN-wide standards for data collection and analysis to help ensure data quality; and develops de-identified public use datasets from completed CPCCRN research protocols. The DCC also monitors the safety and progress of the research studies and has instituted a centralized Institutional Review Board (IRB). CPCCRN funding levels from 2008 through 2013 are shown in Exhibit 3 and include funds for the program site staff, the DCC, approved protocol-related expenses, and limited travel and other costs.

Exhibit 3: CPCCRN Funding by FY: 2008 to 2013

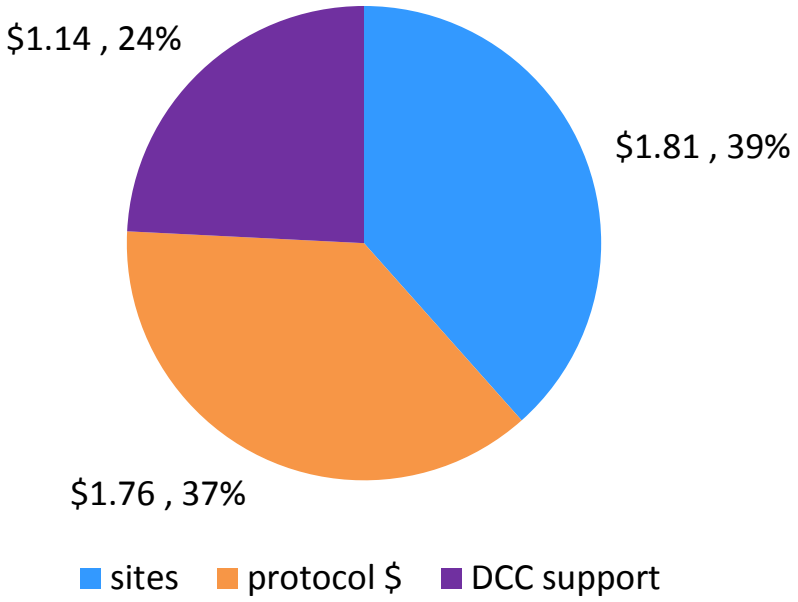


** Clinical sites are funded through the U10 mechanism and the DCC is funded through the U01 mechanism.

The distribution of CPCCRN funds by function is shown in Exhibit 4. The CPCCRN sites each receive some salary support for a PI,

Alternate PI, and a Research Coordinator, and those allocations accounted for 39 percent of the network's 2013 funding. Funds allocated to implement study protocols accounted for $1.76 million, or 37 percent of the network's funding, and the remainder went to support the Data Coordinating Center.

Exhibit 4: CPCCRN FY 2013 Funding by Category



The CPCCRN is directed by a Steering Committee with additional oversight provided by an Advisory Board and a Data and Safety Monitoring Board (DSMB). Oversight is also provided by senior staff at the NICHD which includes a Program Scientist, Network Coordinator, and a Project Officer. The Program Scientist and Network Coordinator provide scientific oversight and leadership, while the Project Officer provides administrative and fiduciary oversight. The Steering Committee is chaired by an independent critical care scientist and meets at least quarterly. The Steering Committee includes the DCC PI and center PIs, Alt-PIs, and Research Coordinators. Other DCC staff members at the University of Utah and NICHD program staff also participate in Steering Committee meetings. The Advisory Board provides community input, and the DSMB monitors the network's clinical trials.

During its history, the network has supported 16 protocols with 6 completed and 10 current studies. Of CPCCRN's 16 past and current protocols, 2 were clinical trials and 14 were observational studies. Three protocols included issues related to family-centered care and/or quality of life while 6 protocols looked at variations in PICU practice patterns. Exhibit 5 shows the protocols that have been funded and conditions investigated type of study, lead site, and status of the study. The two clinical trials are shown in blue.

Exhibit 5: Protocols Implemented in CPCCRN

Protocol	Condition(s)	Type of Study	Lead Site	Current
Bereavement	Complicated grief	Observational	CHOM	
CPRq	Cardiac arrest	Observational	CHOP	X
CQI	Infection	Methodological	SEAT	
CRISIS	Sepsis	Clinical trial	UPMC	
Critical Asthma	Critical asthma	Observational	CHLA	
ECMO/BATE	Thrombosis/ECMO	Observational	PHNX	**
FSS + TOPICC	Not applicable	Methodological	PHNX/ CNMC	X
HIP	Cardiac arrest	Pharmacology	CHOP	X
LAPSE	Sepsis	Observational	SEAT	X
MOTIF	Pain	Observational	ARCH	
PEACE-AZ	Thrombosis/ECMO	Pharmacology	CHOP	**
Pertussis	Pertussis	Observational	UTAH	X
PHENOMS	Sepsis	Observational	UPMC	X
TBI/ADAPT	TBI	Comparative effectiveness	MICH	X
THAPCA	Cardiac arrest	Clinical trial	MICH	X
Ventilation	Acute lung injury	Observational	CHLA	
Core Data project	Not applicable	Not applicable	UTAH	X

** Asterisks mark the two protocols that had not begun enrollment as of winter 2014.

Some CPCCRN institutions also participate in related research programs or organizations such as the Pediatric Emergency Applied Research Network (PECARN); the Pediatric Acute Lung Injury & Sepsis Investigators (PALISI); and the Clinical and Translation Science Award (CTSA) program. Five of 10 current and previous CPCCRN institutions are PECARN sites. The DCC for CPCCRN is

also the DCC for PECARN. Ten current and previous CPCCRN clinical sites are PALISI sites. Six current CPCCRN sites are also CTSA sites.

Purpose of the Evaluation

The CPCCRN is at its ten-year mark and is the flagship network for critical care research at the newly formed NICHD Pediatric Trauma and Critical Illness Branch (PTCIB). The CPCCRN has not been the subject of an independent full-scale evaluation since it was established in 2005. The main objectives of the evaluation were to provide information that will: (1) support NICHD leadership and program managers in making key decisions about the scope, funding level, organizational context, and collaboration and coordination needs of the CPCCRN; and (2) support research planning efforts for the PTCIB.

This evaluation is not designed to assess the performance of the CPCCRN per se; instead, the evaluation will contribute valuable information about CPCCRN's operations and structure to help inform decisions about the program's future. One important limitation is that the CPCCRN program is unique and there is no available comparison program to help support conclusions about how the network should be expected to contribute to the field of pediatric critical care. The evaluation addresses this limitation by considering CPCCRN in relationship to its goals and the expectations of its stakeholders. However, those goals and expectations may be either overly pessimistic or unrealistically optimistic.

Information on CPCCRN's collaboration efforts are essential to the evaluation given the program's multifaceted nature, collaborative design, and the importance of working with others to meet the complex needs of the research field. However, collaborative activity for the program takes place in an environment with myriad constraints and complicating factors, and there is no counterfactual data available to determine how much collaboration "should" occur and through what means. The evaluation addresses this issue by gathering in-depth qualitative data to ensure that the barriers and

facilitators of collaborative activity are identified, understood, and thoughtfully considered.

This evaluation also encounters the limitations inherent in self-reported data from interviews and investigator reports. Such information is subject to desirability and recall bias, among other concerns. The evaluation has been designed to triangulate these data with other sources, such as publications, to address those concerns.

Finally, an important limitation for this evaluation (and all evaluations of NIH research programs) lies in the nature of research, where final outcomes occur only many years after the initiation of research activity. Because treatment strategies and interventions often take decades to make their way into clinical practice, the full contribution of the CPCCRN (a program less than 10 years old) cannot be completely assessed at this time. The evaluation acknowledges this limitation; however, gathering and analyzing information on intermediate outcomes of the network can still be valuable to support scientific planning.

Methodology

Study Questions

As shown in Exhibit 6, the evaluation addressed 9 questions across 4 areas: (1) scope/objectives; (2) coordination/collaboration; (3) network structure; and (4) contributions and leadership.

Exhibit 6: Study Questions

Scope and Objectives 1. What are the most important research needs for the field of pediatric critical care, and how is CPCCRN positioned to address those needs? 2. What challenges do scientists face in conducting pediatric critical care research in particular? How similar are these challenges to other related areas of research? Does CPCCRN address those challenges, and if so, how? 3. What are the implications of constructing the CPCCRN based on a broad versus a narrow scientific scope? Coordination and Collaboration

4. How does the research conducted by the CPCCRN program fit in the context of other pediatric critical care research at NICHD and HHS?
    - Has the NICHD portfolio of pediatric critical care research changed over time, and if so how?
    - What issues need to be considered in balancing the pediatric critical care research portfolio by type of study, by funding mechanism, and other characteristics of the research organization?
5. How has the CPCCRN program collaborated and coordinated with other HHS efforts in the areas of pediatric critical care and emergency care research? Are there ways to strengthen these efforts to benefit the field?

Network Structure

6. What are the advantages and disadvantages of the network's current processes for identifying research questions, designing protocols/projects, and distributing resources across projects and within the network?
    - How do CPCCRN's processes compare with those followed in other NICHD networks?
    - How might expanding or focusing the network affect these processes?

Contributions and Leadership

7. How has the CPCCRN program contributed to the overall literature and scientific advances in pediatric critical care research?
    - How do the publications resulting from CPCCRN compare with the products of other research grants in pediatric critical care?
    - How do subsequent grants resulting from CPCCRN compare with the products of their research grants in pediatric critical care?
8. Has the CPCCRN helped build research capacity in pediatric critical care and if so, how?
9. Has the CPCCRN program played a leadership role in the field, and if so, how? Could this role be strengthened to benefit the research field?

Data Collection and Analysis

The CPCCRN used a multi-method data collection and analysis plan. The evaluation included the following data collection activities:

- Interviews with investigators and staff supported by CPCCRN sites and the DCC;
- Interviews with program staff at NICHD involved with the CPCCRN program;
- Interviews with program staff at NICHD that oversee other NICHD-funded research networks;
- Interview with program staff in the PECARN network;
- Abstraction, review, and analysis of descriptive and performance data on CPCCRN, including publications;

subsequent research grants; leveraging of additional funds; involvement of senior and early-stage investigators; coordination and collaboration with related programs at the NIH and at other HHS agencies; and other contributions to developing enhanced research capacity for the field of pediatric critical care;
- Portfolio analysis of NIH-supported research relevant to pediatric critical care;
- Abstraction of data from IMPAC II and other NIH data bases, the CPCCRN website, and the DCC, including applications, progress reports, population tracking, protocol procedures and reports, and investigator information;
- Expert panel meeting of seven experts in pediatric critical care research to discuss research needs, capacity building, and challenges in pediatric critical care research, and the role of NIH in the support and development of pediatric critical care research; and
- Review of the overall literature related to the research needs and challenges in conducting pediatric critical care research.

Exhibit 7 shows the data collection sources and methods for the CPCCRN evaluation.

Exhibit 7: Data Sources and Evaluation Topics

	Topic	Sources and Methods
The Field	Research needs	Overall literature review; Expert panel; Participant and stakeholder interviews; PTCIB planning meeting
	Research challenges	Overall literature review; Expert panel; Participant and stakeholder interviews; PTCIB planning meeting
	Pediatric Critical Care at NICHD, NIH, and beyond	Portfolio analysis; Expert panel; PTCIB planning meeting; Participant and stakeholder interviews
Structure and Organization	CPCCRN staff and investigators	Progress reports; Financial reports; Investigator NIH grant history; Investigator publication history; Program documents; Participant interviews

	Topic	Sources and Methods
	Protocol selection and priority setting	Program documents (CPCCRN and others); Participant interviews; Interviews with other HSAs from other research networks
CPCCRN at 10 Year Mark	Research projects, recruitment, data sharing	Participant interviews; Program documents; CPCCRN publications
	Leveraged funding	Spinoff grants (IMPAC II); Participant interviews; Program documents; CPCCRN publications
	CPCCRN publications	CPCCRN publications
	CPCCRN's leadership role	Participant interviews; Expert panel; PTCIB planning meeting

Interview Data

Primary data collection for the CPCCRN evaluation included semi-structured interviews with program participants and other CPCCRN network staff to obtain their perspectives on the CPCCRN program and related research fields. To develop interview protocols that were most likely to generate the data and information required to inform the CPCCRN evaluation, the study team initiated a detailed internal design and review process of potential questions. Five different protocols were developed for the CPCCRN study including interviews of (1) PIs, (2) Alternate-PIs, (3) Research Coordinators, (4) NICHD Program Staff, and (5) Other Network Program Officers.

The study team conducted thirty-three interviews with staff in the CPCCRN network, NICHD program staff, and program staff from other research networks. Interviews were conducted with lead CPCCRN investigators (13); the DCC PI (1); Research Coordinators (7); NICHD program staff (3); and Other Network Health Scientist Administrators (9).[1] Scheduling was organized by type of role held in the network, so that all PIs were interviewed first, then Alt-PIs, and finally RCs. Interviews with other network administrators took place after all CPCCRN program staff had been completed.

[1] One network administrator interviewed was from an HHS agency outside NIH.

Interviews were conducted from December 2013 through April 2014. Interview data collected during the CPCCRN study was particularly valuable in understanding participants' perspectives on federal programs, describing program operations and considerations in detail, and assessing program impact.

Analyses were conducted according to the category of interviewees so that CPCCRN investigators and NICHD program staff were analyzed together, as were CPCCRN research coordinators and other network program staff. Various forms of data display were constructed to highlight relationships across questions and for different types of analysis.

NIH Grant Data

Documentation from the CPCCRN program, including applications, progress reports, population tracking, protocol procedures and reports, the CPCCRN website, and other documentation kept by the DCC was used to abstract information on program resources, activities, structure, and impact. IMPAC II was used to obtain information on the amount of funding and other resources allocated to CPCCRN and its collaborating projects. IMPACT II was also used to describe the NIH grant history of CPCCRN investigators. Other NIH data systems were also used to support portfolio analysis of NIH grants related to pediatric critical care and emergency care. Data was analyzed to assess leveraging of other funding sources; methods and mechanisms for collaboration; relationships with other research programs; participation in committees and other elements related to program structure; and activities related to leadership in the research field.

The NICHD analyzes the NIH grant history of investigators and trainees from a variety of programs. This information informs analyses of training programs and research portfolios. NICHD has developed standard operating procedures and pre-programmed databases to help ensure consistency and quality control for analysis of NIH grant data, and these procedures were used for the CPCCRN analysis as well. NIH grant data was analyzed to show trends over time in CPCCRN "spinoff" grants and collaborations, as

well as the characteristics of CPCCRN investigators and institutions.

Overall Literature Review

An overall review of the pediatric critical care literature published 2008-2012 was conducted to provide information on two questions: 1) what are challenges inherent in pediatric critical care research; and 2) what are pediatric critical care research needs. A SCOPUS search identified 1,849 articles, using the relevant search terms listed in Appendix B. Screening by abstract reduced this number to 1,667 articles that were selected for varying degrees of review. Only four articles were intended to specifically address research challenges or needs as such; but it was expected that this information could be found in other articles and all were reviewed. Because an initial screening of 150 randomly-selected articles suggested that heterogeneity of pediatric critical illness could be a research challenge, critical conditions that were the primary focus of an article were grouped and counted in general categories; similarly, research needs were grouped in categories and counted. A limitation of this method was that, given the co-morbid conditions frequently found in pediatric critical illness, the counts indicate overall magnitude but are necessarily imprecise.

NIH portfolio analysis

To place the CPCCRN program and the NICHD pediatric critical care program in context with the overall NIH portfolio in pediatric critical care, a portfolio analysis was conducted to review related NIH grants. The NIH reports to the Congress on research funded in 237 categories. These categories represent widely varying levels of detail – from broad topics like behavioral and social science, to specific conditions like cerebral palsy. Reports on each of these conditions are developed through a text mining system called the Research, Condition, and Disease Categorization (RCDC) system. This method is used to match projects to categories. The research category levels represent the NIH's best estimates of the research expenditures related to a given category, and are the only officially recognized NIH estimates of funding related to specific research topics. Any

figures derived outside this system or related to additional topics are purely unofficial estimates. It should also be noted that the NIH does not use these reported categories for budgeting or planning purposes.

Pediatric critical care is not one of the NIH's official reporting categories, but the broader category of Pediatrics is included. To analyze research expenditures in pediatric critical care, analysts began with the larger Pediatrics category. For each grant reported as part of the Pediatrics category in FY 2013, the abstract and specific aims of the grant application were reviewed by two analysts working independently. A conservative methodology was used to classify grants. A grant was identified as pediatric critical care research only if both of the following conditions were met: (1) the original data were collected on human subjects age 0-21 (i.e. animal studies were excluded); and (2) it was clear from the documentation that the research was specific to a pediatric critical care setting (i.e. PICU). Research on critical conditions that were not treated in a critical care setting were excluded. For this reason, the resulting figures most probably underestimate NIH's investment in pediatric critical care, especially in such areas as pediatric cancer, cardiology, and medical rehabilitation. Research on neonates was included; however, grants dealing with a purely neonatal population were marked as such, to facilitate analysis separating neonatal and pediatric populations. The results of the coding from the two analysts were compared and there was 96.6 percent initial agreement and the few discrepancies were resolved upon further discussion. The resulting data were then described by NIH Institute or Center (IC), grant mechanism, neonatal and pediatric populations, and by topic. Because the NICHD is home to the CPCCRN program, the NICHD pediatric critical care program was analyzed in more detail, including spending trends over time.

CPCCRN Investigators, Protocols, and Publications

CPCCRN investigators were identified through the annual progress reports submitted by each of the CPCCRN sites and the DCC. For each staff member, the following information was abstracted and recorded from each progress report: name; percent effort supported

from the grant in each year; role in CPCCRN in each year; sex; degree; site; years in CPCCRN; and year of first doctoral level degree. If degree information was not included in the progress report, the information was accessed from the NIH IMPAC II database, the CPCCRN web site, the university web site, and materials from the CPCCRN steering committee meetings. A 100% error check was conducted for information on investigators to ensure accuracy. For research investigators, data on NIH grant and review history were obtained from the NIH IMPAC II database. Finally, the Scopus database was searched by the name of each CPCCRN investigator to obtain a full publication history. Publications were verified individually, by both name and affiliation. University web sites, CVs, biosketches, and individual articles were cross-checked as needed.

The DDC is a repository for much of the data and information on the CPCCRN studies, including the 16 protocols that have been implemented since the network's beginning. Of these studies, 10 were ongoing at the time of the evaluation study. The DCC cleans data submitted by each of the clinical sites for each of the studies and maintains a data base by site on numbers of subjects recruited, number that agree to participate, ethnicity, race, age and other demographic and study variables. Along with the study implementation data, the DCC also keeps a database on financial records, including billing by each of the sites typically based on capitation rates specific to each study.

Public use, deidentified datasets are also available from the data coordinating center on six completed projects (CRISIS, CQI, Asthma, MOTIF, Bereavement, and FSS) and core descriptive datasets. Data from CPCCRN studies are generally available after study completion. To enhance the public health benefit of these studies, public use datasets are made available to qualified researchers. Further information about how researchers can access the dataset(s) is available from the CPCCRN website maintained by the DCC at www.cpccrn.org.

Publications from the CPCCRN network were identified by the DCC and confirmed by the progress reports submitted for the network.

Information based on the publications, including citations, was retrieved from Scopus. Journal-specific information, including the journal impact factors, was obtained from the ISI's Journal Citation Reports, by year and journal.

Author information from CPCCRN publications was used to identify characteristics of investigators, and to review networking and collaboration patterns in the CPCCRN and in pediatric critical care research.

Expert Panel

An Expert Panel of non-CPCCRN experts in pediatric critical care was held at the NICHD on May 28, 2014. This panel was established specifically to inform the CPCCRN evaluation. Potential participants were reviewed with priority given to researchers that would represent various specialty areas, publications in pediatric critical care, home institutions, grants and other activities in pediatric critical care research, national and/or international reputations in pediatric critical care, and relationships with CPCCRN sites and investigators or with NIH.

The seven pediatric intensivists on the Expert Panel represented children's hospitals, medical and nursing schools, and universities located in Pennsylvania, Texas, California, Boston, Colorado, and Chicago. Experts were asked to provide an independent perspective on scientific priorities for the field of pediatric critical care research, capacity-building needs for the field, challenges for scientists conducting pediatric critical care research, and how the NIH through CPCCRN and the PTCIB could contribute to advancing the field of pediatric critical care. The Expert Panel session was recorded and a summary report of the discussions was developed.

NICHD and NIH Support for Pediatric Critical Care Research

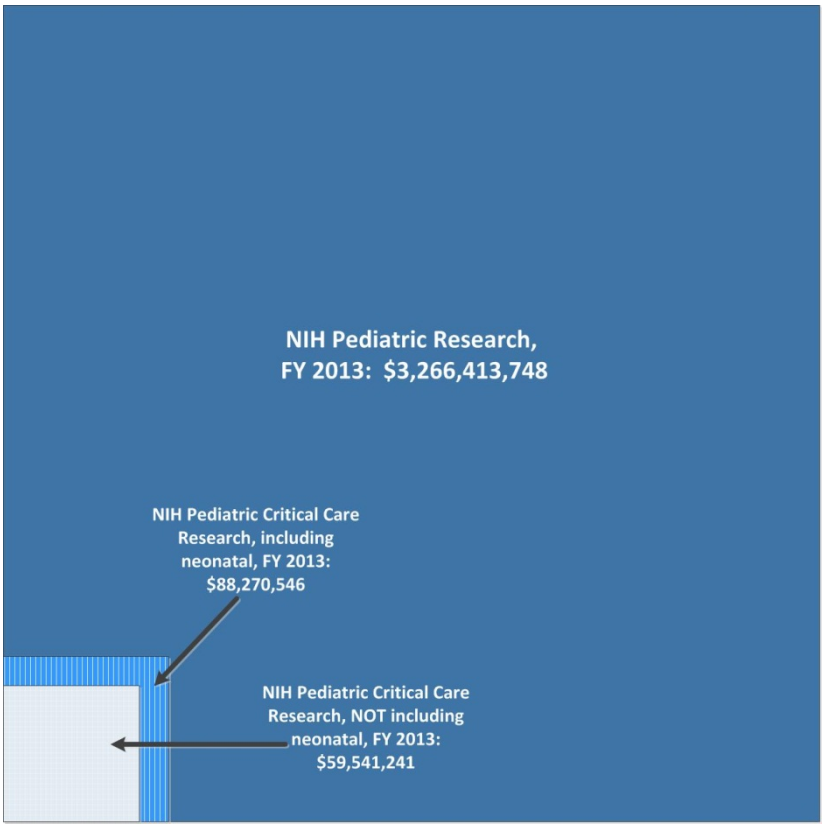
Advances in biomedical research have prompted a revolution in the diagnosis, treatment, and prevention of disease. Children have benefitted greatly from revolutionary progress in biomedical

research, including progress in pediatric critical care. Survival rates in the PICU have increased dramatically over the last several decades. Pediatric research continues to be an NIH priority. The NIH's strong basic research portfolio provides the foundation for pediatric research in a variety of scientific areas, including pediatric critical care.

In fiscal year (FY) 2013, NIH funding for research grants and projects directed specifically at pediatric research amounted to an estimated total of $3,266,413,748. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) funded the largest portion of pediatric research among the 27 NIH Institutes and Centers (ICs), taking a leadership role in many pediatric research efforts that involve trans-NIH collaborations. However, the NICHD alone accounted for only 20 percent of total NIH support for pediatric research. This reflects the breadth of the research portfolio at the NIH dedicated to improving the health of children everywhere.

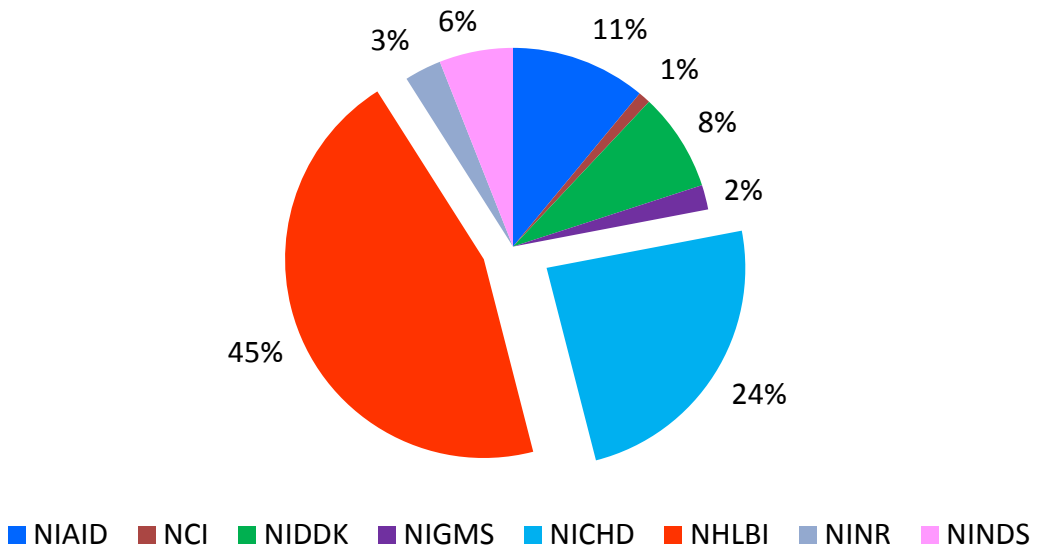
Clinical studies in pediatric critical care form a relatively small but important part of pediatric research at the NIH. As Exhibit 8 shows, in FY 2013 the NIH spent an estimated total of $88,270,546 on pediatric critical care research. Of this total, $28,729,305 was directed specifically at neonatal research and $59,541,241 included pediatric critical care outside the neonatal period.

Exhibit 8: NIH Pediatric and Pediatric Critical Care Research, FY 2013



The $59.5 million in NIH support for pediatric critical care research flows through 8 different NIH institutes, each with a unique mission related to critical care. Exhibit 9 shows how each institute contributes to the NIH support for pediatric critical care research. The largest proportion of pediatric critical care research is supported by the NHLBI, which accounts for almost half. The NICHD supports about one-quarter of the total, with the remaining 6 Institutes combining to support slightly less than one-third.

Exhibit 9: NIH Pediatric Critical Care Research, Excluding Neonatal, FY 2013, by IC



Each institute supports projects in pediatric critical care that are closely aligned with the overall mission of the institute. NIAID supports pediatric critical care research related to genetic susceptibility of life-threatening influenza, lung and liver transplantation in children, and how to care for immunocompromised children in the PICU. NCI's research program in pediatric palliative care for children with cancer includes research in the PICU. NIGMS supports critical care research mainly related to pediatric septic shock. NIDDK's research portfolio includes studies in the PICU of children experiencing liver failure, kidney failure, and diabetic ketoacidosis. NINR research focuses on nursing care in the PICU, including palliative care. NINDS research centers on caring for patients in the PICU with seizures or trauma, particularly traumatic brain injury.

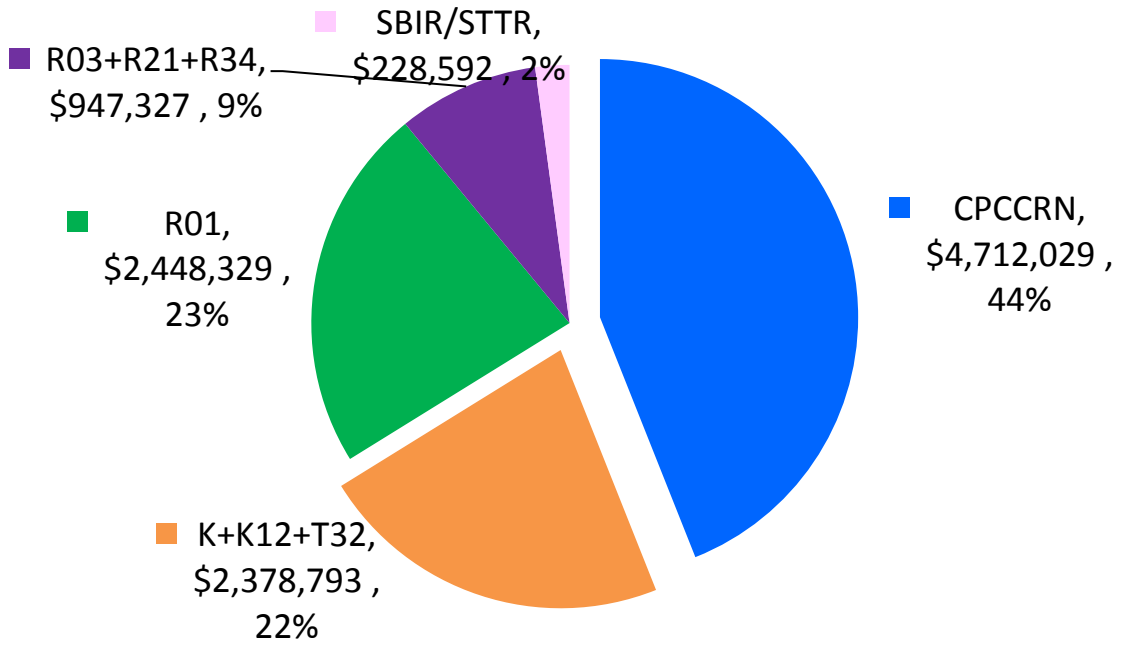
NHLBI's research portfolio in pediatric critical care emphasizes cardiac conditions, both congenital conditions and those that arise from other causes such as trauma or infection. For example, one of NHLBI's larger projects focuses on cardiomyopathies (diseases of the heart muscle). Cardiomyopathies are a leading cause of heart

failure, death, and heart transplantation in children. Scientists are looking to identify specific cardiac biomarkers that will help determine the most appropriate evidence-based clinical care for pediatric cardiomyopathy patients, including when to consider heart transplantation as a therapeutic option. Other NHLBI projects focus on how to address the heart and lung complications of pulmonary hypertension, how to assess lung capacity in critically ill children with cystic fibrosis, and how to improve care for children undergoing blood and bone marrow transplants.

Consistent with its broad mission addressing many diseases and conditions in children, the NICHD pediatric critical care portfolio is cross-cutting, addressing multiple organ systems and a wide range of diseases and conditions. In addition to the CPCCRN network, the NICHD's critical care research portfolio includes studies on pediatric brain injury, sepsis, burn injuries, the psychological effects of critical illness, and resuscitation. The NICHD also supports research related to pediatric pharmacology and pediatric medical devices in the PICU.

As shown in Exhibit 10, training and career development grants are also an important part of the NICHD pediatric critical care portfolio. The NICHD portfolio includes the Pediatric Critical Care and Trauma Scientist Development Program, a national faculty training program that develops successful pediatric critical care and pediatric trauma physician scientists. The NICHD also supports individual career development grants in pediatric critical care. CPCCRN, however, accounts for slightly less than half of the portfolio and remains NICHD's major program in pediatric critical care.

Exhibit 10: NICHD Pediatric Critical Care Research Portfolio, FY 2013



Research Priorities and Challenges in Pediatric Critical Care

Scientific Priorities For Pediatric Critical Care

There was little agreement among experts in the field regarding how to select research priorities in the field of pediatric critical care. PIs and co-investigators in the network identified various ways that priorities have been established. One approach was prioritization in terms of specific diseases and to look at understanding the path of physiology of the specific disease. A different approach to prioritizing research topics was to look at diseases and conditions that seemed to result in the most mortalities and then next, the amount of morbidity caused by the condition. Still another approach to prioritization was to investigate procedures that are very common and that are used in the ICU, but in which there is not much known about the right way to do it or the efficacy of doing it. An example is the use of mechanical ventilation in pediatric

critical care. Other cross-cutting topics of interest to the pediatric critical care community were also identified as key research priorities.

Pediatric critical care physicians and nurses treat children with a large number and wide variety of different diseases and conditions. This diversity of conditions was reflected the priorities identified by the CPCCRN investigators, expert panel members, and the overall literature review. Dozens of diseases, conditions, and organ systems were mentioned by CPCCRN participants and members of the expert panel. Nearly 600 (594) distinct diseases or conditions were mentioned in the overall literature as research priorities. One publication reported the results of a survey of pediatric intensivists, and 132 "key" topics and 77 "priority" topics were identified. A list of the topics identified in the literature as research priorities is included in the overall literature review in Appendix C.

Only one topic or category was identified by the majority of CPCCRN participants as a key research priority – sepsis. Sepsis is an often-life threatening, whole-body inflammation illness caused by severe infection. Sepsis emerged as a key priority in the literature and was identified as a priority by the expert panel. Interviewees reported that sepsis was having the greatest impact on children in crisis and that it was a significant challenge to staff in intensive care units in terms of saving children's lives. Sepsis can be caused by a broad spectrum of different types of organisms (such as viral, bacterial, fungal, and protozoan). Repercussions can cause multiple organ failures in a critically ill child and/or septic shock. There is not a single antibiotic or steroid that can be counted on to get good results in every child with sepsis; rather there are hundreds of interactions that may need to be treated and many possible treatment approaches. As one respondent explained, "*We treat the symptoms, but we've yet to be able to stop sepsis… There are too many kids that are either dying or having significant morbidity ….*" Virtually every major organ system was described by investigators and panel members as a priority area for critical care research. CPCCRN participants and expert panel members mentioned respiratory illnesses, such as pneumonia, bronchiolitis, acute lung injury, or Acute Respiratory Distress (ARD) syndrome. Treatment

may involve use of a ventilator to ensure adequate oxygen for blood levels and to the lungs and other vital organs. Cardiac and neurological issues were also mentioned, as damage to the heart and nervous system can result in death or long-term morbidity in children. Trauma, including traumatic brain injury (TBI), was frequently singled out, especially among physicians and nurses who frequently treated trauma patients.

As noted, answers by the interviewees more often reflected their individual personal experiences in the PICU. There were wide variations across the sites and the priorities named appeared to be influenced by the specific training and backgrounds of respondents' roles as PI, Alt-PI, RC, or NICHD program staff. When asked to identify research priorities, one respondent said, "*It's just really hard because there are so very many. Pediatric critical care is such an eclectic specialty; there are so many disorders and conditions of children of all different ages that we take care of. It's not just one disease that we study. All of them really need investigation.*"

In addition to specific diseases and conditions, cross-cutting topics and treatment approaches were identified as priorities in the literature and by CPCCRN participants and expert panel members. When asked whether new technologies or currently used clinical interventions should be rigorously tested for use in the PICU and if so, how these could be identified, one respondent said, "*They all need [testing.] We've been a research-poor subspecialty for years.*" Another pointed out, "*…it's trying to use adult technology to apply to a child who we too often view as a little adult in that particular domain. It just doesn't always work that way, so we really need more technology startups that begin with the needs of the child and the initial work is done tailored to the needs of that patient population, not adapted from what's been developed in the adult.*" A CPCCRN investigator made a similar association with the need to structure research around children and stated, "Outcomes research in the context of pediatric critical care is incredibly important. It's just got to be part of our view of value in the current healthcare environment."

Pediatric critical care processes identified as priorities for further study included: Cardiac surgery; ECMO (Extracorporeal Membrane Oxygenation); general medical surgical interventions in an ICU; mechanical ventilation; resuscitation; bone marrow transplants; drug prescription and drug delivery to critically ill children; ventricular assist devices or lung support devices; and the implications of genetics to all childhood severe illness. Investigators said they understand that pediatric patients are not small adults and cautioned that pediatric critical care research had historically come from how adults had been treated, or through animal experiments, since at one time getting approval for research on children was difficult. Respondents noted that research on advances in technology has been slower in pediatrics. Concern was expressed when the needs of the child had not been adequately addressed and adult experience with technology was simply adapted for the pediatric population.

Other cross-cutting issues that arise within the context of the PICU were also identified as priorities for research. These included how developmental changes in children may impact how they respond to treatments known to be effective for other pediatric or adult patients; subpopulations of patients receiving pediatric critical care that make it difficult to investigate the impact of treatments provided; or how the process of critical care may vary from PICU to PICU and thus complicate interpretation of research findings. Other issues, if addressed, that would contribute to research findings in the complex PICU environment looked at the use of genomics and epigenetics to improve diagnosis and treatment of critical care; more and better data that would create a stronger evidence base to further develop policies and programs for this care; and improved management of large amounts of data common to PICUs. Another overarching concern was the post-survival status of pediatric patients who leave the PICU and whether or not they have long-term medical, psychological, and/or serious disability issues that they and their families will need to address for the long-term or for a lifetime. Respondents reported a commitment on the part of PICU staff to provide family-centered care and said that this is regarded as an integral part of the family and patient's experience.

Scientific Challenges in Pediatric Critical Care

According to the literature review and the CPCCRN participants, the combination of the critically ill patient population and the unique, complex environment of the PICU creates special challenges for pediatric critical care research. Pediatric critical care researchers face similar challenges as pediatric clinical researchers generally: obtaining funding, developing outcome measures, and arranging patient follow-up, for example. Among CPCCRN participants, the most frequently cited challenge was obtaining funding. Participants also identified the need for standardized outcome measures, a limited number of trained clinician-scientists, and the need for expert research support staff. Moreover, some CPCCRN participants and expert panel members stated that as an emerging field of science, pediatric critical care field lacks prestige and a "research culture". One CPCCRN PI related that the field used to be inhospitable to research in general, but he believes this is changing as the number of research studies has grown.

CPCCRN participants, expert panel members, and the literature also described a series of research challenges that were more specific to the patient population and environment of pediatric critical care. There was considerable agreement about these challenges and how they affect research.

In the literature and in participant interviews, the population of pediatric critical care patients was described as small. While large-scale pharmaceutical trials may include as many as 10,000 participants, for most conditions treated in the PICU there will be many fewer patients available for enrollment. Moreover, the patient population is likely to be very heterogeneous, which creates challenges for study design. Even patients with the same diagnosis will vary considerably in their developmental stage (from infants to teens), the severity of illness, whether they suffer from comorbid conditions (especially chronic diseases), and their previous care and treatment before arrival in the PICU.

The literature, CPCCRN participants, and the expert panel also pointed out a series of challenges arising out of the complex

pediatric critical care practice environment, in which patient comorbidities and the "criticalness" of life-threatening patient conditions create a fast-paced, pressured atmosphere. Physicians are expected to individualize care to produce the best outcome for each individual patient, which can make implementing standardized protocols a challenge. Moreover, practice variation is reportedly very high across PICUs and even among intensivists within the same institution. This variation makes it difficult to compare an intervention to the "usual standard of care", when the usual standard is highly variable. In addition, the fast-paced environment may make gathering data on clinical practice, for research or quality improvement purposes, more difficult.

Several participants pointed out that pediatric critical care physicians are generalists because they treat every organ system in the body, and this can make it difficult to develop specialized expertise required to conduct research in multiple areas. *"It's a challenge trying to be an expert and conducting trials in bereavement, CPR, hypothermia, after cardiac arrest, and sepsis. That's a challenge as opposed to being in a [heart network] …where you sort of understand all of the problems …much more innately than you do in critical care."*

Ethical issues were also an important concern, including difficulties in establishing clinical equipoise and in securing informed consent from parents who are often under severe emotional stress.
The interview respondents and Expert Panel members agreed that a network structure can help ameliorate the challenges for the field of pediatric critical care research. Most felt that the challenges were consistent across PICUs. Exhibit 11 lists the challenges and respondent comments about those challenges.

Exhibit 11: Scientific Challenges in Pediatric Critical Care

Challenge	What Participants and Expert Panel Members Reported
Funding	• "Time directed towards identifying appropriate funding sources and obtaining support takes away from research"
Time	• "Lack of protected research time in the PICU"; • "High clinical load in conflict with research time"; • "Time to develop young investigators into those likely to receive grants"
Population Issues	• "Small overall population size"; • "Heterogeneity of disease/condition and developmental stage"
Trained/Skilled Staff	• "Having the cadre of people that have the skillset, energy and passion may be the most important--more so than money"; • "As a relatively new field, we may not have adequate numbers of qualified investigators to answer the questions that research needs to ask"
PICU Environment	• Complex, fast-paced; • "Interventions adopted before adequate research"; • High risk of adverse events; • High practice variations across PICUs
Ethical and IRB issues	• Consenting for vulnerable children and for when the family is in crisis; • "Investigators must put needs of child first" in decisions whether to continue with a research protocol • Determining what level of risk is acceptable; • Getting protocols approved by IRBs; • Follow-up requires IRB approval
Interest/Value as a field of study	• Not always perceived as valuable; • Even though the field has a major impact on population health —"interest and prestige sometimes get lost"
Research Environment	• Not always supportive of research; • "At one time the field was very anti-research, but now this has changed"

Research Capacity-Building in Pediatric Critical Care

Interview respondents and Expert Panel members identified a number of areas where increased capacity is needed in the field of

pediatric critical care research. Within the context of a strong network structure like CPCCRN, those interviewed identified: (1) human capital--the need for more trained and skilled staff, including young researchers to develop with the field; (2) data and informatics—including the need for common data elements; and (3) infrastructure support to conduct more pilot and scaled-up clinical trials. Exhibit 12 shows what specific areas identified for further development within these three categories.

Exhibit 12: Research Capacity-Building Issues

Human Capital Needs	Development of Data and Informatics
• Research training	○ Patient registries/large scale datasets
• Talented support staff trained in pediatric critical care	○ Bio-repositories
• Career development	○ Electronic Health Records (EHR)
• Interdisciplinary collaboration	○ Bioinformatics
• Support for long-term follow-up	○ Common data elements
• Need for 24/7 coverage for physicians and support staff	○ Standardized case definitions
• Researchers trained in basic science and emerging areas (epigenetics, e.g.)	○ Statistical methods and statistical support
• Infrastructure to Support Clinical Trials	○ Data quality issues
• Large number of sites	○ Alternative study designs
• Ensure adherence to protocol	○ Modeling and simulation
• Pilot and scaled-up trials	○ Artificial Intelligence software to identify correlations, anomalies in large data sets
• Identifying determinants of consent	○ Benchmarks for outcome measurement

Human Capital

The need for more trained staff was seen as both a capacity-building for the field and infrastructure issue specific to the CPCCRN. PICUs have focused on the clinical care of critically ill

children of a wide variety of ages—including infants older than 30 days (younger infants with critical illness are typically treated in a Neonatal Intensive Care Unit (NICU)), young children, and adolescents up to typically age 18. Pediatric intensivists have received special training in pediatric critical care medicine for the sickest youngsters, but many not have also received adequate training in research. Said one PI "…I would say first is training.… I think you have to look at how training programs are positioned… to train physicians entering our field in certain areas of research interest. And I would just editorialize that I don't think that the requirements--the strictness of the requirements through training--are sufficient to ensure that programs are imparting that skill set into trainees. So that's number one." Other participants shared similar concerns.

CPCCRN participants and expert panel members strongly emphasized a critical need for more highly trained support staff in pediatric critical care, especially specialized nursing staff. In the CPCCRN network the nurse research coordinator is responsible for day-to-day implementation of the research protocol, including training of bedside nurses, supervising the patient enrollment process, monitoring data, and providing quality assurance for each of the research protocols being implemented at the site. Research coordinators often come in nights and weekends to review admissions and identify potentially eligible study candidates and to supervise implementation of protocols as needed. Both clinical research expertise and advance practice nursing skills are required.

Also needed to build the field of pediatric critical care research is acknowledgement and support for continuing career development for both physicians and other research staff. One interviewee stated: *"How do we take someone with good research ideas and train them to translate those research ideas into good research questions? We have to make sure our young physician scientists have training, funding, and support and are motivated to go forward."*

Another area for building capacity is ensuring skillful interdisciplinary collaboration in both research and clinical care

between pediatric intensivists and clinicians in other biomedical specialties. For example, neurosurgical post-operative care, moderate to severe respiratory diseases, multi-system diseases, hematologic/oncologic diseases, and/or complications of sickle cell crisis may each require that the attending PICU physician consult with other physician specialists about treatment for seriously ill children.

Data and Informatics

Of particular interest were the issues specific to data development and informatics. Health informatics deals with the resources, devices, and methods required to optimize the acquisition, storage, retrieval, and use of information in health and biomedicine. Health informatics tools include computers, clinical guidelines, formal medical terminologies, and information and communication systems. This is a developing area throughout much of medical research. CPCCRN has instituted a Common Data Project that was designed to be a registry of all the ICU admissions each year within the network and their diagnostic categories. Generated by the DCC, the datasets helped investigators calculate sample sizes and ensure that the right types of patients were available for a specific study. The registry is used to support CPCCRN's planning process. It also helps to advance the science by determining how to best collect data from multiple institutions electronically and utilizing the electronic health records.

The Common Data Project began to address data development and informatics in its earlier stages with expectations that it may evolve overtime to a more complex data system in support of the network. Study participants also proposed development of bio-repositories, advanced/common electronic health records, bioinformatics, other common data elements, and more quality controls on datasets.

Another area where more development is needed is in the area of statistical design for research on small populations. Several investigators in both the interview cohort and the expert panel made strong claims for needing alternative research designs to support pediatric critical care research, in order to address the

challenges that arise from small, heterogeneous patient populations and considerable practice variation.

Clinical Research Infrastructure

Interviewees expressed the need to build capacity to support clinical research and clinical trials, although the number of trials and the timing for conducting large scale trials was discussed from many perspectives. Several expert panelists suggested that preliminary research was needed first; other panelists and interviewees suggested scaling up successful pilot studies to larger scale trials.

Participants and panelists agreed that clinical trials are best supported with a network structure, because a network provides the expertise in both research design and study logistics that is needed. For example, researchers noted that informed consent can be a difficult issue in the environment of a PICU. However, due to the expertise of the Research Coordinators, CPCCRN has shown the ability to achieve strong consent rates for families of eligible children despite these challenges. (A review of consent rates obtained from the DCC and analyzed by NICHD for Cycle 2 protocols found that about 73% of eligible subjects were enrolled, excluding one outlier protocol where sampling was used.)

Overall, investigators said that they believe the capacity of the CPCCRN to engage families in the research process has been effective. "*Many of us deal with different communities with different perceptions of research, and I think we have dealt with it in the sense of developing some metrics, so that we know how we are doing in terms of patients or families approaches, and how successful we are. And, we've shared amongst ourselves things that each one of us might have found more helpful in our situations any way in getting families to consent to studies. I think one of the ones we have been fortunate enough to deal with has been education of our nursing staff. Because I think that made quite a bit of difference to where the families might consent to going into studies, because they often trust the bedside nurse.*"

CPCCRN Processes and Operations

This section addresses network structure, including: operations of the network sites; the roles of the NICHD Project Scientist, the DCC, PIs, and Research Coordinators (RCs) in selecting research topics; processes and criteria for selecting research priorities; protocol development; and development and use of common data elements. This section also addresses what can be learned from other NICHD research networks through an understanding of their processes and structures.

Day-To-Day Operations

The CPCCRN sites fund the clinical and research expertise of its PIs and alternate PIs at 10% to 20% of their time. Full-time coverage at each CPCCRN site is provided to the RC, who plays a pivotal role in the network's daily operations. RCs are highly trained nurses who on average have served their site for more than 3 years, the longest for over 7 years. When interviewed for the study about their primary activities, the RCs reported the following responsibilities and how they addressed them in Exhibit 13.

Exhibit 13: Day-to-Day Responsibilities for Research Coordinators

Day-to-Day Activities	What the RCs Reported
Enrollment/ Screening/Consent	• 24-hour/7 days a week screening –"Hard to outsource recruitment of patients to other nurses or fellows." • "Insure that all communication lines are open between various physicians that work with patients" • Parent/patient education provided by RCs, PIs, and physicians
Data Collection and/ or Data Entry	• "Requires a high level of attention to detail' • Train PICU staff on data collection and recording to reduce errors at the data entry level • "Some RCs have support staff for data entry or electronic data systems that can draw from electronic medical records"

Day-to-Day Activities	What the RCs Reported
Provide CPCCRN study requirements and progress at staff meetings	• "Perceived high level of staff awareness about CPCCRN studies" • "Good buy-in from staff and a culture of trying to grow research" • Findings shared directly with nurses and attending physicians in the PICU; at the nurses' station; via email or education binder shared with nurses; at monthly hospital research conferences
Work with IRBs – local IRB and/or central IRB at the DCC	• DCC develops submission for central IRB; RCs continue to report some patient information to their local IRBs • "An expedited process due to the central IRB and role of the DCC" • Follow up on patients and families requires IRB approval
Manage Budgets	• Review study invoices and once approved by PIs, send to DCC • Co-manager of research-related contracts • No RCs reported developing capitation rates • Several RCs reported doing some cost projections and cost management
Answer Queries about the Study	• Day-to-day implementation of the protocol relies on the RC • "Eyes and ears" of the PI • "Must be careful when answering questions to not bias parents in any way about participating in the study"
Train Hospital Staff regarding the Study Protocol(s)	• RCs are highly involved in protocol implementation at almost every level and must ensure that hospital staff adhere to protocol implementation

RCs handled the majority of the day-to-day work for study implementation. Both PIs and Alt-PIs reiterated the importance of the RCs' skill and dedication to promoting the research environment in the PICUs. RCs expressed 24/7 commitment to enrolling subjects and also reaching out to other hospital staff to promote the screening required to enroll the desired number of patients in a study. RCs reported no major difficulties in recruiting patients. One RC explained that they record all new patients on a large white board daily and that study enrollment including screening is a top priority. RCs also provide day-to-day coordination

of the study and oversee protocol implementation and consistent data collection. Working with the support of the CPCCRN on-site medical team, RCs are often the first to identify problems or issues about implementation of a study protocol. They also communicate extensively with the DCC in submitting approved invoices, capitation and related enrollment information, and documentation for local and centralized IRB approval. RCs recognize the difficulties in enrolling subjects in the PICU, but said they have developed special expertise to meet these challenges.

> *"One must make sure that all communication lines are open between the various physicians that work with the patients, and they must be able to communicate to parents that the research won't negatively impact the care of their child. It all boils down to parent/patient education from the Research Coordinator, PIs, and physicians."*

> *"It is hard to outsource the recruitment of patients-- nurses or fellows cannot always page the Research Coordinator at the drop of a hat when an eligible patient is admitted."*

RCs also provide frontline involvement with parents and families of critically ill children in the PICU. RCs said the following (Exhibit 14) about working with parents and families to implement research protocols, the ethical challenges, and the focus on family-centered care.

Exhibit 14: Research Coordinators: Working with Parents

<table>
<tr><th>Working with Families to Implement the Research Protocol</th><th>Ethical Challenges</th><th>Family-Center Care</th></tr>
<tr><td rowspan="2">"Families are encouraged to ask questions and staff to go back several times to see if parents have additional concerns. Also, parents can ask questions of bedside nurses."</td><td rowspan="2">"Families understand the voluntary nature of the studies and are aware that the care for the child will be the same as a non-participant."</td><td>"Most of the RCs reported that families are involved in hospital rounds."</td></tr>
<tr><td>"The level of involvement depends on the family; some are more engaged than others."</td></tr>
</table>

Working with Families to Implement the Research Protocol	Ethical Challenges	Family-Center Care
"Staff must be careful when answering questions to not bias the parents in any way about participation by giving too much unsolicited information."	"If a family doesn't fit into the study, you have to respect the parents' decision."	"The focus in the PICU is on family-centered care."
"Our PIs are super-involved. The PI will introduce himself to families. I watch for any protocol violations. And we look out for patients."	"The requirements of the questionnaires and surveys can be burdensome to families and at times families may be pushed to do them even if they aren't in a good position to do so due to their child's condition. The research team should be very sensitive to this when asking parents to respond to questionnaires."	"The RCs have become the frontline in interacting with patients and their families, and have become much more connected and involved with families."
"Many studies now are not consent studies and just require data collection study waivers."		"However, the family's main concern is with the child's clinical care and the study data is secondary to that. As long as they think their child is getting the best/adequate care, it makes them more willing to participate in the study. Anything we can do for the family, we do. For example if there are other siblings, one of the hospital social workers can arrange for needed child care."

Role of the NICHD Project Scientist

The NICHD Project Scientist is responsible for ensuring that research ideas generated by the CPCCRN are consistent with NICHD and NIH priorities, comply with NICHD and NIH requirements, and do not duplicate existing research efforts. The Project Scientist is responsible for coordinating CPCCRN's efforts with the overall critical care program at NICHD and with broader research efforts related to critical care at the NIH and beyond. The Project Scientist also brings their own scientific and administrative expertise to the network.

Role of the CPCCRN DCC

The DCC PI has intimate knowledge of the research field and plays an important role in establishing research priorities, along with the site PIs and the Project Scientist. The DCC's role is to help develop the research design and data collection procedures so that the study is carried out effectively. As one respondent reported, "*For this particular network the DCC role has been critically important and extremely valuable…. They take a central role both in how we refine the design of the trial [and] how we ultimately execute it.*" The DCC is mindful of human and financial resources along with practical logistics, and contributes experience in both these areas to the priority setting process.

Comparison of Roles Reported in Other Networks

Roles of PIs, Project Scientist, and the DCC in the six other NICHD research networks interviewed by the evaluation team are described in this subsection. The team conducted semi-structured interviews with one--and for two of the networks two-- Health Scientist Administrators (HSAs) from the following six NICHD research networks: (1) Reproductive Medicine Network (RMN); (2) Maternal-Fetal Medicine Units Network (MFMU); (3) Pelvic Floor Disorders Network (PFDN; (4) Obstetrical-Fetal Pharmacology Research Unit Network (OPRU); (5) Adolescent Medicine Trials Network (ATN) for HIV/AIDS Interventions; and (6) Neonatal Research Network (NRN).

In the case of the two networks in which two HSAs were interviewed, responses duplicated each other and therefore have been reported as single responses. Exhibit 15 reports whether or not the PIs, Project Scientist and DCC for each of these other networks had voting rights and rights of review in the prioritization and protocol development process. Like CPCCRN, the decision making process was centered around periodic Steering Committee meetings although the ATN has a modified committee process.

Exhibit 15: Roles in Setting Priorities: Other Networks

Participants with Vote or Role in Setting Research Priorities, as Reported by Health Science Adminstrator			
Network	**PIs**	**Project Scientist**	**DCC**
PFDN	x		
MFMU	x	x	x
OPRU	x		x
NRN	x	x	x
ATN		x	
RMN	x	x	x

There were similarities across the networks regarding the roles of the PIs, Project Scientists, and the DCC:

- PIs were most likely to originate ideas for research and develop those ideas into protocols.
- Project Scientists were likely to be equal partners on the Steering Committee, providing input about research priorities and important research questions.
- The DCC provides input on research design, statistical feasibility, and required project elements. They are often involved in the protocol development phase as well as review. HSAs reported that two of the DCCs are not involved in the process to identify research priorities.

In the PFDN the Steering Committee Chair has instituted the Delphi method with open voting where prioritization is determined by PI voting with each having three votes. Voters can use all votes at once, split them across protocols, or give them to a team member to

use. If voting is close, protocols with fewer votes are eliminated for a re-vote on the remaining protocols. This network also reported using voting for abstract and manuscript prioritization in support of their DCC's availability. Protocols are vetted and developed through a Protocol Team chaired weekly by the PI who has introduced the concept.

MFMU also uses a Prioritization Committee to further develop each protocol with the PI of the proposed Study, the DCC PI, staff, several investigators, and NICHD. The Project Scientist gives the final approval to completed protocols. The OPRU network starts with a long list of drugs to be studied in pregnant women and then prioritizes which drugs to study. The Project Scientist in this network has the final vote on selected studies. All studies from this network must also submitted to the Food and Drug Administration (FDA) for approval and may also require submission of an Investigational New Drug (IND) Application.

The NRN HSA said that priorities may be driven by the most recent RFA (Request for Application) which included a broad statement requesting trials of agents and strategies to improve short and long term outcomes for infants. The RMN used to identify key priorities in the RFA but no longer does so, giving those on the Steering Committee more leeway in its prioritization process. The RMN Project Scientist works with the Steering Committee to decide which concept proposals go forward to their Advisory Board of outside experts who then gives recommendations to the Steering Committee.

The ATN reported a unique process for establishing research priorities. Their grant sites are focused on long-term services to adolescents with HIV so that the research behind this is not the site PIs' main focus. Unlike other networks, the sites are adolescent medicine providers and are used primarily as recruitment sites and to retain their adolescent subjects over multi-year cycles. The research agenda for the ATN is outlined in the RFA as priority research areas for each five year grant cycle. Protocols are submitted after the application process with an internal review by NIH leadership. The ATN Coordinating Center (ACC) was

established as separate from their clinical sites and their DCC and is the group that establishes scientific priorities for this network. The scientific leadership meets with the NIH collaboratively to develop the protocol concepts as a group. Protocol concepts come forward every six months and each is presented and voted on at the network meetings. Two site PIs sit on the ACC. There is also a community group of adolescents that forms the Community Advisory Board (CAB) who has a role in reviewing aspects of proposed protocols. Protocols are fully developed within a hired scientific leadership group that has three subgroups. All protocols come back to the NIH program staff for approval.

Unlike the CPCCRN participants, some respondents interviewed about other networks discussed tensions between the clinical sites and the DCC. Most tensions seemed to occur because the DCC had limited time and resources to address all of the immediate needs of the networks. There was also disagreement about roles and governance, and some communication problems were reported. One respondent said, *"Right now this is a big problem. Everybody has their territory in terms of what their contract or grant is for. Having a firm outline of the roles and responsibilities for the PI and the DCC is important."*

Processes for Setting Research Priorities for CPCCRN

CPCCRN participants described four criteria used to select the network's research priorities:

(1) investigator interests or expertise;
(2) scientific importance to the field;
(3) practicality of carrying out the research; and
(4) biggest impact on the lives of children.

There was agreement that it was best to use the expertise within the network to make these kinds of difficult decisions so that experts can review each other's work and make sure that the appropriate questions and issues for the network are addressed. Another criteria identified by several interviewees was the role of the Project Scientist in setting the research priorities for the network.

Protocol Development, Review, and Vetting in the CPCCRN

CPCCRN investigators and program staff reported a detailed process for developing study protocols which includes significant reviews by the Project Scientist, the Steering Committee, and the Data and Safety Monitoring Board (DSMB). PIs or Alt-PIs may introduce a concept paper for consideration by the Steering Committee at one of the four quarterly meetings. Investigators at the meeting, the DCC PI, and the Project Scientist raise questions about the study's purpose, related research, statistical implications, and preliminary design. Exhibit 16 shows the sequence of major steps for vetting protocols as reported by those interviewed for the evaluation study.

Exhibit 16: Review and Approval of Protocols within CPCCRN

CONCEPT PAPER PIs develop a concept paper and deliver it to Steering Committee in advance of review meeting
VOTE Steering Committee vote on whether to develop concept into a protocol
MINI-PROTOCOL A mini-protocol or its equivalent is prepared for presentation to the committee
REVIEW AND FEEDBACK Mini-protocol is presented to Steering Committee for feedback
FULL PROTOCOL PI prepares full protocol, using feedback from DCC, Project Scientist, others.
VOTE Full protocols receive a prioritization vote or go into a queue for final funding
DATA AND SAFETY MONITORING BOARD (DSMB) Full protocols receive a final review from a DSMB (or other external Advisory Board) for finalization.
GETTING INTO THE PIPELINE Approved protocols may go into the pipeline until the network is ready and able to implement another research protocol. Once resources have become available for a new study, decisions must again be made about which study will be implemented next. This means that the order a study gets into the pipeline will not necessarily determine order of implementation.

For the most part, the CPCCRN vetting process is internal. However, external presenters have been invited to seek the network's participation in trials that are going to be funded through non-network sources.

For CPCCRN protocols, study cost estimates are based on the study protocols and is spearheaded by the DCC, with input from the investigators as well as the RCs who review all protocols carefully to ensure that the step-by-step implementation process has been adequately defined.

Participants said that they were well-aware of the capitation process and how this impacts the research. It is considered part of the prioritizing process. Said one investigator, "*Well, I mean we kind of just have a model that everyone goes through when they present their protocol they have to present a capitation model. So they're expected to budget out what they think the protocol is going to cost in terms of laboratory equipment, just laboratory billing, research billing, X-rays, anything that's going to be involved with the data collection they have to cost that out. Then they submit it to the steering committee and we talk about …… what would be a reasonable capitation charge so that the costs are covered, or do we have funding anywhere else that can cover some of these costs."*

Several respondents stated that capitation rates are set based on how many dollars are available. There was agreement that the network does not have enough protocol dollars to make the capitation model completely rational. In one study there were cost problems after implementation. A study participant said that they did not have enough money to get a specimen shipped for analysis or for putting information before the IRB. The solution was to revisit how much the network was paying for the specimen analysis and the DCC ended up increasing the sites' capitation funds. Part of the solution was to also reallocate how the DCC was giving out the capitation funds, so that sites, especially the smaller sites, had more upfront money to get their IRB requirements done. In speaking of capitation rates, one PI explained: *"I think they are done by a general assessment of how much work is required by the*

project and by how much money is required by the participating institutions to stay afloat with regard to all studies. I think that the capitation rates are used very well, not only to capitate studies, but also to ensure that the institutions get the appropriate funding to get everything done. The advantages are that the more patients you enroll the more money you make. The disadvantages are that there's a capitation on the capitation with the yearly enrollments so that high-enrolling institutions are limited."

Investigators said that implementation of new studies typically goes smoothly thanks to the advance training on the protocol that all network staff, including RCs, receive. Steering Committee meetings are used as training opportunities for the RCs so that all receive consistent information on protocol implementation and other study activities. The DCC manages the recruitment data for the network and, with one exception, data shows that recruitment of subjects by the network has been at about 73%. According to those interviewed, the establishment of a strong consenting process and consistent implementation of study protocols has made the CPCCRN network attractive to outside researchers. When there have been problems with consenting that may have been specific to a certain site, leadership in the network has shared what has worked at their site to develop this skill more evenly across the clinical sites.

Common Data Elements and the Core Data Project

Common data elements enable clinical investigators to systemically collect, analyze, and share data across the research community. The CPCCRN Core Data Project provides pilot and descriptive data necessary for hypothesis generation, study design, preliminary power analyses, and recruitment projections for studies under development by the CPCCRN. The DCC initiated the Core Data Project as a registry of all the ICU admissions each year within the network. It looks at patient's diagnostic categories at discharge to help investigators calculate sample sizes and to ensure that the right types of patients would be available in the participating PICUs to do a particular study. Said one respondent about the Core Data Project, *"It's great. It's helped a lot. What it did was for us to have all that information of all the hospital and ICU admissions and the*

different ICD-9 codes and everything has helped immensely with our planning." Investigators referred to the Core Data Project as the 'cube' where they could estimate sample size and see how many patients, for example, they have admitted with a specific condition. The project is an effort to understand the patient resources within the 17,000 admissions of the network. It's used when looking at a grant they wanted to fund or a study they wanted to conduct within the network. At the start of the network, the Common Data Project was often the only way to get some idea about the numbers needed with any research project. However, some participants reported that the lack of homogeneous domains makes generalization of common data elements difficult.

There was agreement that conceptually the common dataset is important and at least one respondent felt it could be made a little more robust. He discussed mining the data that is already available and refining its format to make the dataset richer. Another respondent commented that the dataset is very helpful and that it has met its intended uses. Another respondent concurred and said that the data is being collected and used for a purpose within the network and at some point should become available for public use. As long as the data is de-identified, others agreed that it could be shared with qualified researchers outside of the network. The DCC does release Public Use Datasets to qualified researchers that are made available after study completion and that include de-identified data derived from completed CPCCRN research protocols.

Lessons Learned from Other Networks

Other NICHD networks had mostly similar processes to prioritizing research within the network. The evaluation team interviewed the HSAs in those networks and found the following similarities across most of them:

- Discussion and selection of projects was done via Steering Committee.
- There was a strong role for NICHD Project Scientist.
- There was a similar role for the DCC.

Differences in the other networks showed that scientific scope was limited by a well-defined population being served and the conditions that addressed the populations' needs in the research. The role of strategic planning/priority setting efforts was different in a number of the outside networks where the HSA seemed to exercise more oversight in the decision making process. There were also differences in how capitation rates were set. As discussed earlier in this section one network used its project sites for recruitment so that its decision making process in terms of research prioritization did not rely on PIs and was unique to the cohort interviewed. Exhibit 17 reports similarities and differences to the CPCCRN network processes.

Exhibit 17: Process Steps by Network

Other NICHD Networks Interviewed	Process Within the Steering Committee						
	Concept Paper	Vote	Mini Protocol	Review & Feedback	Full Protocol	Vote	DSMB
PFDN	x	x	x	x	x	X	X
MFMU	x	x	x	x	x	X	X
OPRU			x	x	x	X	X
NRN	x	x	x	x	x	X	X
ATN**					X	X	
RMN	x	x			x	X	X

****** The ATN Coordinating Center (ACC) was established as separate from their clinical sites and their DCC and is the group that oversees the establishment of scientific priorities for this network. The ACC PI hires scientists to do protocol generation. Ultimately the Executive Committee which is the ATN Steering Committee makes the final approvals of protocols that come out of the ACC process.

In addition to the interviews of HSAs from other networks, the evaluation team considered these and other NICHD pediatric networks in terms of research focus, annual grant award, number of clinical sites and number and type of research being conducted**.** Exhibit 18 describes other pediatric research networks and compares them with CPCCRN.

Exhibit 18: NICHD Pediatric Research Networks

Program	Number of Sites	2013 $ (Base)	Current Protocols	Types of Protocols
ATN (HIV/AIDS)	14	$20.4 M	5	Clinical trials (3/5); observational (2/5)
MFMU (maternal-fetal)	16	$15.9 M	6	Clinical trials (5/6); observational (1/6)
NRN (neonatal/ NICU)	18	$11.8 M	9	Clinical trials (6/9); observational (3/9)
ACE (autism)	8*	$8.1 M*	5	Clinical trials (7/8); observational (1/8)
GN (international maternal-fetal)	7	$8.1 M	4	Clinical trials (3/7); observational (4/7)
CPCCRN (pediatric critical care)	7	$4.7 M	8	Observational (6/7); clinical trials (1/7)
OFPU (obstetric pharmacology)	4	$4.4 M	3	Pharmacokinetics (3/4); clinical trials (1/4)

Out of the seven networks described in the exhibit, most have a more-narrowly defined research agenda, such as autism, obstetric pharmacology, neonatal health, or maternal fetal health. The networks supporting the most clinical trials include ATN, MFMU, NRN and ACE. CPCCRN is funding the most observational trials.

Collaboration with Other Research Networks

Interviewees reported that networks can learn from each other in terms of study design and processes such as data management, data transfer from one institution to another, and how to conduct studies efficiently. PECARN was recognized as a larger network with a different funding model. PECARN deals with pediatric emergency care research while CPCCRN addresses pediatric critical care research. However, investigators and some program staff felt that PECARN and CPCCRN are interrelated with some common issues, such as issues that affect both the emergency department and the PICU, like the THAPCA study where both networks have participating sites. Also, PECARN and CPCCRN have the same PI who directs the DCC for both networks. A few CPCCRN

investigators expressed an interest in having a joint meeting about once a year to talk about key areas that are shared by both networks. According to one interviewee, PECARN ended up adopting the CPCCRN's approval process after several years of using a subcommittee approval process. Staff said that they could learn from each other. PECARN also has strong interest in trauma and trauma-related projects which is a significant research interest of the CPCCRN.

The Pediatric Acute Lung Injury and Sepsis Investigators network includes clinical researchers from 78 PICUs in North America. Its mission is to identify supportive, preventive, and therapeutic strategies for acute lung injury, sepsis, multi-organ failure, and other acute life-threatening pulmonary or systemic inflammatory syndromes that affect infants and children. A number of CPCCRN investigators reported that they participate in PALISI which is recognized for its commitment to collaboration with other investigators; its open meetings to discuss research ideas, protocols and other interests; providing direct feedback from the network and the Scientific Steering Committee; participating in multi-center research studies; enhancing investigator skills; and nurturing young investigators and those highly experienced. CPCCRN investigators reported that PALISI generates a lot of new ideas and gives a lot of feedback. It provides an opportunity to access community researchers and institutions.

CPCCRN investigators have also interacted with the Clinical and Translational Science Award (CTSA) program. One investigator reported serving on the search committee for a new PI for the CTSA and on the Scientific Advisory Committee. CPCCRN investigators said that they have interacted with the UPMC's CTSA program for a substantial amount of infrastructure for teaching, education, trial work, and statistical design. According to CPCCRN respondents, some of this information has found its way back to the CPCCRN Steering Committee when they have used the statisticians or other resources from the CTSA. Another CPCCRN investigator reported keeping in touch with CTSA so that they know what studies CPCCRN is doing and CTSA staff have been known to send support services or help in problem solving. Another said that he had

leveraged the informatics team and leveraged study design input and expertise from their bio statistics and epidemiology research design core.

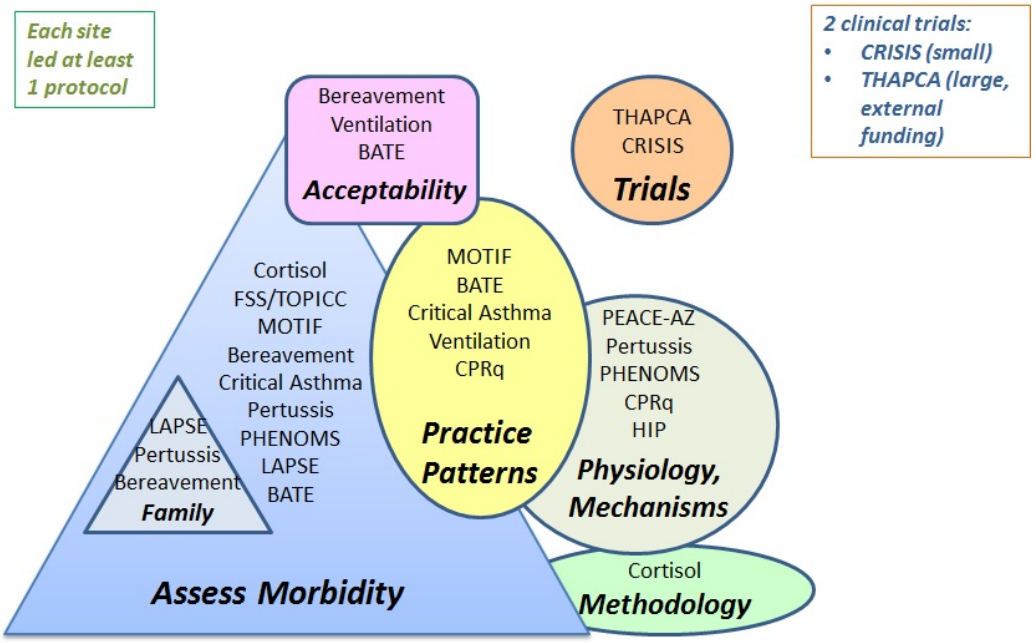
Characteristics and Productivity of CPCCRN Research

Characteristics of CPCCRN Protocols

The CPCCRN program was designed with a very broad charge in mind – "to investigate the efficacy of treatment and management strategies to care for critically ill and injured children, as well as to better understand the pathophysiological bases of critical illness and injury in childhood."[2] As described previously, the field of pediatric critical care is exceptionally broad in terms of the number and diversity of research needs. Program participants also characterized the field as exceptionally challenging due to the varied needs of a heterogeneous group of patients. Therefore it is perhaps not surprising that the CPCCRN protocols are also highly variable, covering a wide range of conditions involving nearly all the major organs in the body. Exhibit 19 shows the range of topics and types of research in CPCCRN protocols.

[2] CPCCRN Request for Applications, http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-14-022.html, issued March 20, 2014.

Exhibit 19: Topics and Types of Research in CPCCRN Protocols



Note: some studies are included in more than one category.

The bulk of CPCCRN studies are observational studies, and many are designed to assess the morbidity of pediatric critical care patients. For example, the Life After Pediatric Sepsis Evaluation (LAPSE) project is a prospective observational study to describe short and long-term outcomes among a cohort of children surviving septic shock. LAPSE is designed to assess the intensity and duration of persistent sepsis-associated morbidity, through repeated measurements of health related quality of life and functional status. In the Bereavement project, CPCCRN researchers measured the incidence of complicated grief in bereaved parents at 6 and 18 months. The Functional Status and TOPICC projects were designed to develop outcome measures based on morbidity.

Along with assessing morbidity, several CPCCRN projects measured variation in practice patterns among PICUs within the CPCCRN. The Measuring Opioid Tolerance Induced by Fentanyl (MOTIF) study showed that PICUs varied greatly in baseline opioid doses, average daily or total doses, or peak infusion rates across PICUs. In the Critical Asthma study, CPCCRN investigators documented large

variation between sites in the management of critical asthma, including mechanical ventilation in pediatric patients.

As is often the case with research in an emerging field, CPCCRN studies built on each other, and new studies were designed and implemented to address concerns that arose during the protocol design process. For example, from the start CPCCRN investigators were eager to conduct research on sepsis and septic shock, a leading cause of death in the PICU. However, as the investigators moved closer to designing protocols for studies of sepsis, they encountered a technical roadblock. A crucial intermediate variable in the study of sepsis is the level of cortisol, a stress hormone. To assess how sepsis infections progress in young children, periodic cortisol measurements are required in real time. However, existing methods for measuring free cortisol required substantial lead time. As a result, the CPCCRN investigators did not launch a full-scale sepsis protocol as initially planned. In the interim, they conducted the Cortisol Quantification (CQI) study to evaluate adrenocortical function in children with sepsis and septic shock. CPCCRN investigators developed and validated an ultracentrifugation method that enables free cortisol quantification within 2 hours. This method enabled rigorous study of adrenocortical function in new studies of pediatric sepsis. Similarly, in the bereavement study, several smaller sub-studies needed to be conducted to develop and validate measures to assess physician and parent perspectives on information provided to parents following the death of a child. Finally, the negative result of the CRISIS clinical trial directly led to the design of the PHENOMS study, where researchers sought to identify characteristics that might explain differential response to treatment in critically ill children with sepsis.

Later in the history of CPCCRN, the network gravitated towards more studies involving physiological mechanisms underlying critical illness. These studies still fit in the category of observational research, but the research is designed to identify and better understand physiological mechanisms of disease that might provide crucial clues to designing personalized treatments. For example, the Inflammation Phenotypes in Pediatric Sepsis Induced Multiple Organ Failure (PHENOMS) is a prospective observational cohort

study to enroll 400 children with severe sepsis to test the hypotheses that children with specific sepsis phenotypes have; 1) increased mortality, 2) predisposing genotype and environmental risk factors, and 3) increased CRP and Ferritin levels that correlate with clinical outcome. As part of the Critical Pertussis study, CPCCRN researchers partnered with an NIH basic science laboratory to improve understanding of the genomic and biological underpinnings of pertussis.

Recognizing the importance of family-centered care for children with critical illness, several CPCCRN studies have incorporated research questions related to the family context. Although the Bereavement study is the most obvious example, the Critical Pertussis and LAPSE studies also include family-centered variables.

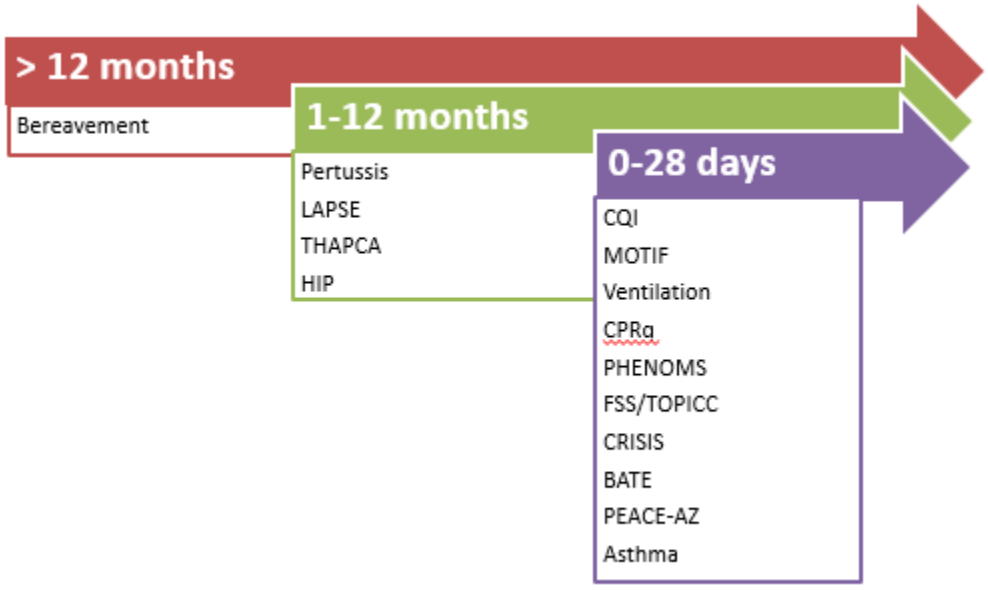
Although CPCCRN's mission begins with the purpose statement about "to investigate the efficacy of treatment and management strategies …", the network has funded only 2 clinical trials in its first 10 years. The first of these, the Critical Illness Stress-induced Immune Suppression (CRISIS) trial, was supported purely with CPCCRN funds. The CRISIS study assessed "prophylaxis" strategies used to prevent stress-induced nosocomial infection and sepsis. The study used a double-blind, randomized, controlled trial design to test the hypothesis that daily prophylaxis with metoclopramide, zinc, selenium, and glutamine would reduce nosocomial infection and sepsis in critically ill children. The study was terminated for futility after enrollment of 293 subjects.

The second clinical trial, Therapeutic Hypothermia After Pediatric Cardiac Arrest (THAPCA), is actually two related trials; one study will assess the hypothermia treatment in-hospital, and the other in out-of-hospital setting. The THAPCA clinical trials aim to determine whether therapeutic hypothermia, in which the body's temperature is lowered and maintained several degrees below normal for a limited period of time, is as successful at treating children who experience cardiac arrest as it has been in treating adults. The THAPCA project will evaluate therapeutic hypothermia's efficacy at increasing survival rates and reducing the risk of brain injury in infants and children who experience a cardiac arrest while out of

the hospital or in the hospital. The THAPCA project arose from CPCCRN investigators and the preliminary work was done within CPCCRN. However, the bulk of the planning for THAPCA was supported by a NICHD clinical trial planning grant, and the main study is supported by a larger R01 grant from NHLBI. CPCCRN's funding level is not sufficient to support the THAPCA trial. CPCCRN's protocol funds for the entire network would be insufficient to support THAPCA in its peak expenditure year, even if the network devoted the entirety of the protocol funds to THAPCA alone. Nonetheless, according to the investigators and as documented in the summary statement for the main THAPCA grant, the expertise and infrastructure CPCCRN provided to the THAPCA trial were essential to the success of the funding application.

CPCCRN's studies typically involved a short follow-up period, encompassing either PICU discharge, hospital discharge, or a short period thereafter. As Exhibit 20 shows, most CPCCRN studies follow patients for one month or less. The longest follow-up period was for the Bereavement study, and several others had a one-year timeline. Of note, the studies with the longer time frame were not universally the most expensive studies. However, the CPCCRN studies with a longer time frame were among the studies that received external funding.

Exhibit 20: Patient Follow-up Periods for CPCCRN Studies

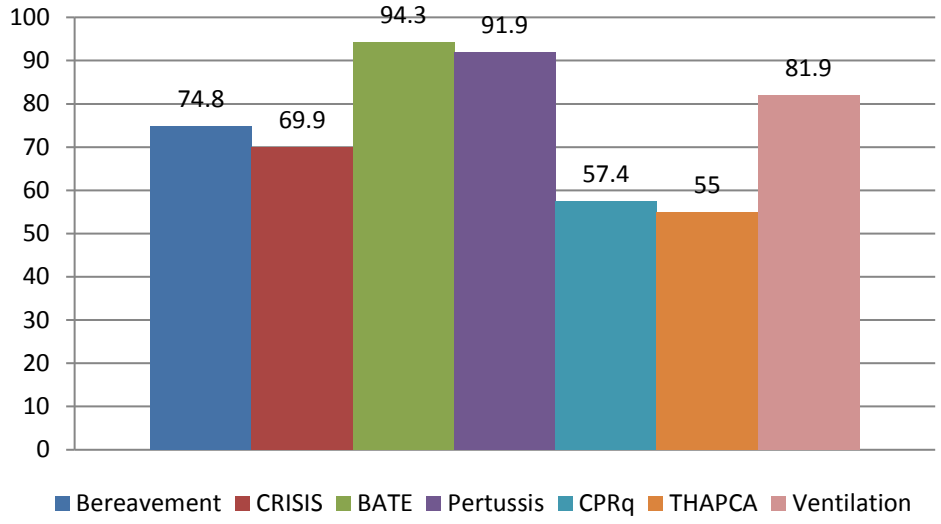


Enrollment in CPCCRN Protocols

Pediatric critical care researchers face a difficult challenge in enrolling critically ill children in clinical trials. Parents must be approached, at what must be one of the most difficult moments in their lives, and asked to participate in a research study while their child is seriously ill and in danger of death. Especially if the study involves randomization, parents may have difficulty trusting that the child will receive the best possible care. The CPCCRN Research Coordinators, however, were fully confident of their expertise in this delicate task. Recruitment data on CPCCRN research protocols supported the confidence of the research coordinators. Excluding one protocol where a sampling method was used, CPCCRN enrolled 73% of eligible subjects in cycle 2 protocols.

Exhibit 21 shows the percent of eligible subjects enrolled in CPCCRN studies, by protocol. In two of these studies – THAPCA and pertussis – the study included both non-CPCCRN sites and CPCCRN sites. In both cases, the CPCCRN sites had significantly higher enrollment yield compared with the non-CPCCRN sites.

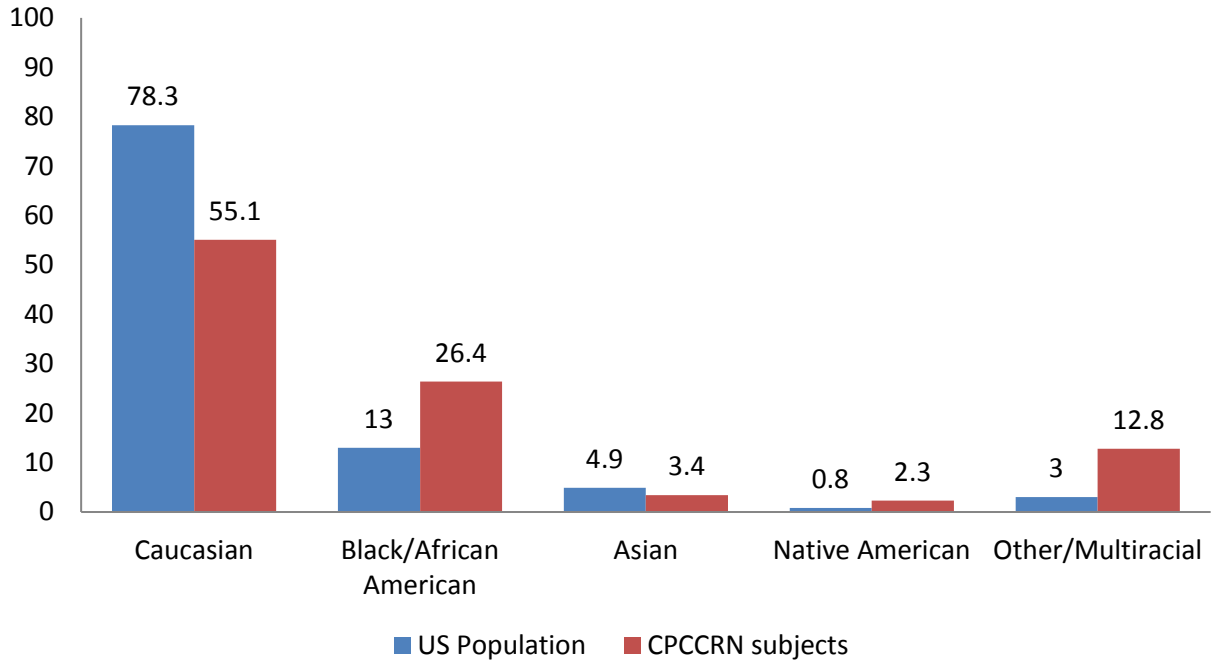
Exhibit 21: Percent of Eligible Subjects Enrolled, by Protocol



A number of factors typically influence the number of eligible subjects enrolled in a study – the size of the potential participant pool, inclusion and exclusion criteria that determine eligiblity for a protocol, the nature of the study, and the skills of the individuals charged with presenting research opportunities to potential participants. For example, it is unsurprising that the THAPCA and CPRq study had a relatively low yield compared to other protocols, because those protocols were associated with serious emergency conditions, or had challenging exclusion criteria. There was some variation across CPCCRN sites in the overall participant yield, but the differences in the percent of eligible subjects was considerably smaller. Variations across sites in overall number of participants were strongly associated with the overall size of the PICU.

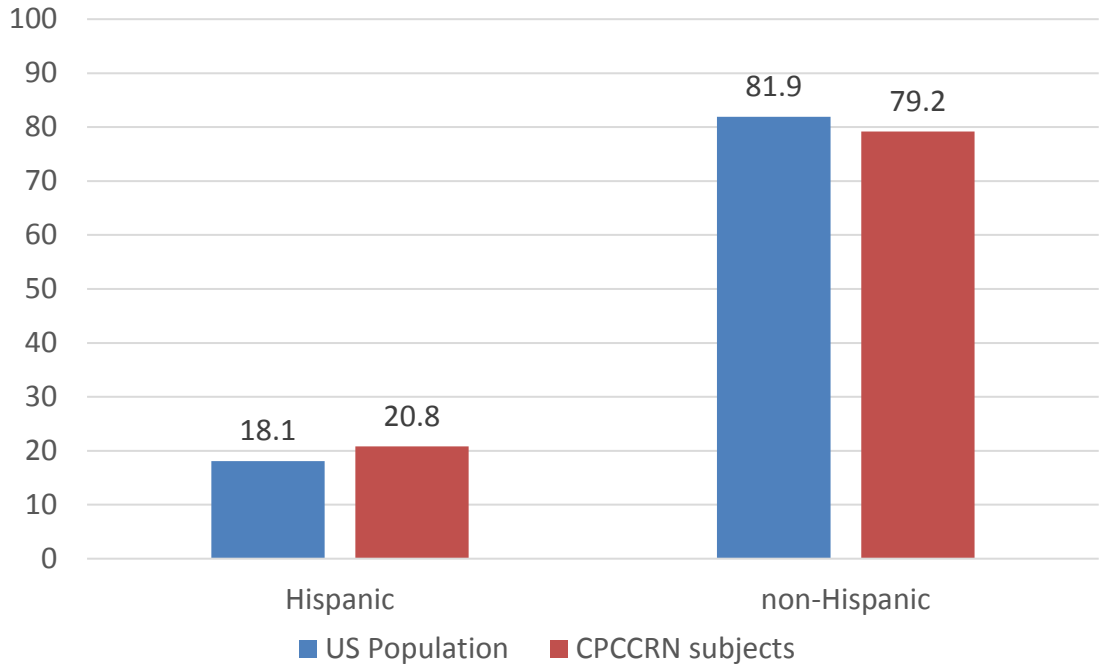
The racial and ethnic diversity of the population is an important consideration for CPCCRN. The CPCCRN sites were selected, in part, to ensure that studies can be conducted with a diverse population. Exhibit 22 shows the racial diversity of CPCCRN subjects compared with the U.S. population, indicating that CPCCRN studies include a racially diverse group of participants. Exhibit 23 shows the ethnic makeup of CPCCRN subjects, indicating that CPCCRN studies are similar to the U.S. population in the inclusion of individuals of Hispanic origin.

Exhibit 22: Racial Diversity of CPCCRN Subjects and U.S. Population



Note: for CPCCRN subjects, the data above exclude cases where information was not available.

Exhibit 23: Ethnic Diversity of CPCCRN Subjects and U.S. Population



Note: for CPCCRN subjects, the data above exclude cases where information was not available.

Scientific Publications Resulting from CPCCRN Studies

Exhibit 24 shows the CPCCRN publications by study. The bereavement protocol yielded the most publications. Of note, the THAPCA study, which had not yielded clinical results at the time of this analysis, yielded 7 publications, reflecting widespread interest in the study even in its relatively early stages.

Exhibit 24: CPCCRN Publications by Project

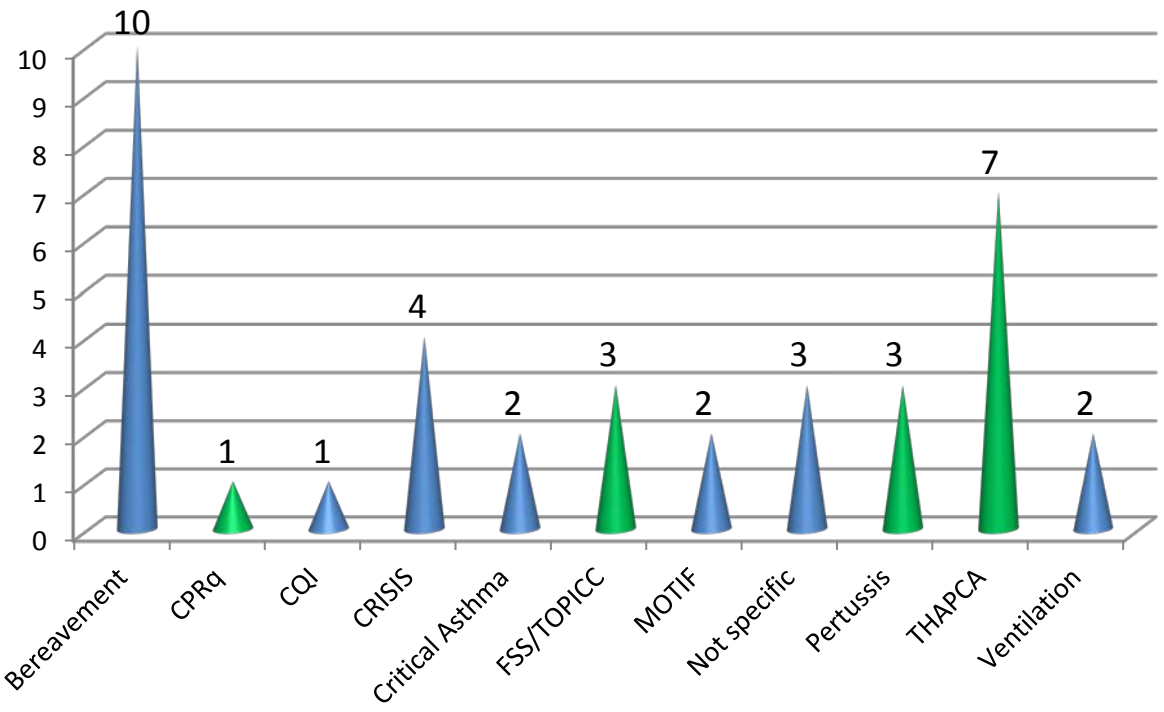


Exhibit 25 shows CPCCRN publications by journal. CPCCRN publications have appeared in pediatrics journals as well as critical care and specialty journals. The journal *Pediatric Critical Care Medicine* accounted for more than half of CPCCRN's total publications. None of CPCCRN's publications appeared in a journal with an impact factor greater than 7.0.

Exhibit 25: CPCCRN Publications by Journal

Journal	5 Year Journal Impact Factor	Number of Articles	Percent of Articles
Pediatric Critical Care Medicine	2.692	20	52.6
Critical Care Medicine	6.404	5	13.2
Journal of Palliative Medicine	2.446	2	5.3
Journal of Pediatrics	4.281	2	5.3
Pediatrics	6.112	2	5.3
Archives of Pediatrics and Adolescent Medicine/ JAMA Pediatrics	4.742	2	5.3

Journal	5 Year Journal Impact Factor	Number of Articles	Percent of Articles
Communication and Medicine	Not available	1	2.6
Genome Announcements	Not available	1	2.6
Intensive Care Medicine	Not available	1	2.6
Journal of Palliative Care	1.144	1	2.6
Journal of Parenteral and Enteral Nutrition	3.397	1	2.6

Exhibit 26 shows CPCCRN articles with citations. Of note, the two most-cited articles, and three of the five most frequently cited publications, are related to the THAPCA study. Nearly one-quarter of CPCCRN articles had no citations (articles published less than one year before the analysis were excluded).

Exhibit 26: CPCCRN Articles with Citations

Article Title	Year	Journal	Citations
Multicenter cohort study of in-hospital pediatric cardiac arrest	2009	Pediatric Critical Care Medicine	75
In-hospital versus out-of-hospital pediatric cardiac arrest: A multicenter cohort study	2009	Critical Care Medicine	53
Weaning and extubation readiness in pediatric patients	2009	Pediatric Critical Care Medicine	47
Tolerance and withdrawal from prolonged opioid use in critically ill children	2010	Pediatrics	18
Multicenter cohort study of out-of-hospital pediatric cardiac arrest	2011	Critical Care Medicine	17
Collaborative Pediatric Critical Care Research Network (CPCCRN)	2006	Pediatric Critical Care Medicine	11
The collaborative pediatric critical care research network critical pertussis study: Collaborative research in pediatric critical care medicine	2011	Pediatric Critical Care Medicine	8
Critical care for pediatric asthma: Wide care variability and challenges for study	2012	Pediatric Critical Care Medicine	8
Critical pertussis illness in children: A multicenter prospective cohort study	2013	Pediatric Critical Care Medicine	6

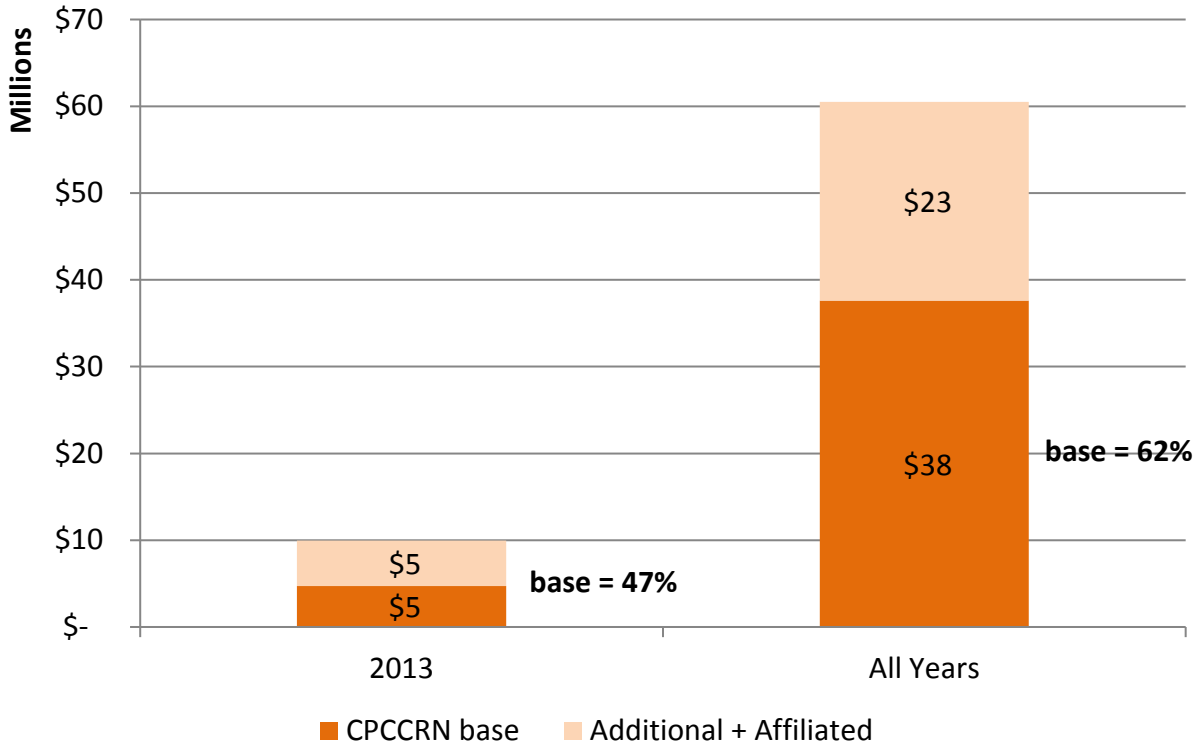
Article Title	Year	Journal	Citations
Parents' Perspectives Regarding a Physician-Parent Conference after Their Child's Death in the Pediatric Intensive Care Unit	2007	Journal of Pediatrics	5
Rationale and design of the pediatric critical illness stress-induced immune suppression (CRISIS) prevention trial	2009	Journal of Parenteral and Enteral Nutrition	5
Accounting for medical communication: Parents' perceptions of communicative roles and responsibilities in the pediatric intensive care unit	2009	Communication and Medicine	5
Ratio of PICU versus ward cardiopulmonary resuscitation events is increasing	2013	Critical Care Medicine	4
Parents' perspectives on physician-parent communication near the time of a child's death in the pediatric intensive care unit	2008	Pediatric Critical Care Medicine	4
Complicated grief and associated risk factors among parents following a child's death in the pediatric intensive care unit	2010	Archives of Pediatrics and Adolescent Medicine	3
Opioid analgesia in mechanically ventilated children: Results from the multicenter measuring opioid tolerance induced by fentanyl study*	2013	Pediatric Critical Care Medicine	3
Fatal and near-fatal asthma in children: The critical care perspective	2012	Journal of Pediatrics	3
The randomized comparative pediatric critical illness stress-induced immune suppression (CRISIS) prevention trial	2012	Pediatric Critical Care Medicine	3
Functional status scale: New pediatric outcome measure	2009	Pediatrics	3
Baseline serum concentrations of zinc, selenium, and prolactin in critically ill children	2013	Pediatric Critical Care Medicine	3
Therapeutic hypothermia after pediatric cardiac arrest trials: The vanguard phase experience and implications for other trials	2013	Pediatric Critical Care Medicine	3
Follow-up study of complicated grief among parents eighteen months after a child's death in the pediatric intensive care unit	2011	Journal of Palliative Medicine	2

Article Title	Year	Journal	Citations
Is "rescue" therapy ethical in randomized controlled trials?	2009	Pediatric Critical Care Medicine	2
Variability in usual care mechanical ventilation for pediatric acute lung injury: The potential benefit of a lung protective computer protocol	2011	Intensive Care Medicine	1
A framework for conducting follow-up meetings with parents after a child's death in the pediatric intensive care unit	2011	Pediatric Critical Care Medicine	1
Collaborative pediatric critical care research network: Looking back and moving forward	2010	Pediatric Critical Care Medicine	1
Ethical and logistical considerations of multicenter parental bereavement research	2008	Journal of Palliative Medicine	1
Physicians' conceptualization of "closure" as a benefit of physician-parent follow-up meetings after a child's death in the pediatric intensive care unit	2013	Journal of Palliative Care	1
Early postresuscitation hypotension is associated with increased mortality following pediatric cardiac arrest	2014	Critical Care Medicine	1
Early lactate elevations following resuscitation from pediatric cardiac arrest are associated with increased mortality	2013	Pediatric Critical Care Medicine	1

Leveraging of External Funding

Because of CPCCRN's limited budget and the cost of conducting clinical research, CPCCRN participants stressed the need to leverage external funding sources. In 2013, CPCCRN-affiliated projects received more funding from other sources than they did from the CPCCRN base funding. Exhibit 27 shows the estimated base funding and leveraged funding for CPCCRN-affiliated projects, in FY 2013 and over the lifespan of the CPCCRN network.

Exhibit 27: Estimated Base and Leveraged Funding



Nine of 16 CPCCRN-affiliated protocols were supported partially or entirely with non-CPCCRN dollars. Eight of CPCCRN's 38 research investigators have received additional funding for CPCCRN-affiliated projects. For two studies with outside funding – THAPCA and ADAPT – protocol costs for each study alone exceeded CPCCRN's $1.76 million total allowance for all protocol costs for the network.

Sources of CPCCRN leveraged funding are shown in Exhibit 28. Seven protocols were funded entirely with CPCCRN funds – CPRq, CQI, CRISIS, FSS/TOPICC, MOTIF, BATE, and PEACE-AZ. Two protocols were associated with unsuccessful NIH grant applicatons – Bereavement (to NINR) and BATE (to NHLBI).

Exhibit 28: CPCCRN Leveraged Funding for Protocols

Protocol(s)	Funding from …
ADAPT (TBI)	NINDS
Bereavement, LAPSE, Mechanical Ventilation	NICHD
Critical Asthma	BPCA
HIP, THAPCA	NHLBI
Pertussis	HHS, NIGMS (in-kind)
PHENOMS	NIGMS
Total of 9 protocols	**6 funding sources**

Data Sharing: Public Use Datasets

Public use datasets were available from CPCCRN's data coordinating center on 6 completed projects—CRISIS, CQI, Asthma, MOTIF, Bereavement, and FSS—along with a portion of the CPCCRN core descriptive dataset. According to the DCC, few requests have been received for these data, but data were provided in all cases.

Leadership Role for the Field

CPCCRN participants stressed the leadership role of the network. CPCCRN participants stated that CPCCRN plays a leadership role for the field as a whole by:

- Conducting important research projects;
- Increasing the visibility of the field to scientists, funding organizations, and the public at large; and
- Promoting a supportive research culture in the individual CPCCRN sites and in the field at large.

The expert panel members agreed that it is important for CPCCRN to play a leadership role. Some members, however, were not familiar with CPCCRN and its activities although they were experts in the field of pediatric critical care. Expert panel members expressed a need for increased visibility for the network.

Considerations for the Future of CPCCRN

As described earlier, CPCCRN shares some structural and functional features and characteristics with other NICHD clinical research networks. In discussing CPCCRN's future, current participants and members of the expert panel shared a range of ideas about how they believe the network can best serve the field. These ideas can be characterized through 4 possible network types:

- an "adaptive" network, characterized most by flexibility;
- a "pilot studies" network, designed to focus on preliminary clinical and/or observational studies to lay the groundwork for more definitive clinical trials;
- an "observational studies infrastructure" network, designed to provide a framework, resources, and infrastructure for pilot and larger-scale observational research; and
- a traditional "clinical trials network", intended to support definitive clinical trials to provide the evidence base for changes in clinical practice.

Each of these types of networks offers distinct advantages and disadvantages, requires different considerations, and would be assessed using different measures. There was no clear consensus on what type of characteristics CPCCRN should adopt, but insights were offered on the advantages and disadvantages of various strategies. Types of options for CPCCRN's future are discussed below, based on the insights of network participants and expert panel members, discussions in the overall research literature, and the results of CPCCRN's first two funding cycles.

Adaptive Networks

Several CPCCRN participants emphasized the flexibility of CPCCRN as one of its key assets. An "adaptive" research network takes an approach designed to quickly and efficiently take advantage of scientific opportunities as they arise. Such a network requires flexible decision making processes, to allow researchers to focus on emerging scientific areas, contribute to urgent public health problems, and take advantage of new funding opportunities as they become available. CPCCRN participants pointed out the network's leveraging activities as evidence of how an adaptive network can

contribute to the field. One PI stated that because the field of pediatric critical care has so many research needs, it also has many research opportunities and there are many ways for the network to contribute. An adaptive network may define goals very broadly, and would operate with limited strategic planning. Projects would need not relate thematically to each other, as long as they were making key contributions.

An adaptive network offers several obvious advantages – the ability to leverage additional funding and adapt to the rapid pace of scientific change, for example. One expert panel member pointed out that such a structure may be well suited to an "emerging" scientific field like pediatric critical care that has many diverse needs. This scientist stated that strategic planning for such a field may have limited payoff, because there are so many needs. He suggested that the resources that would go into research planning would be better spent on research costs for a program with a flexible, rapid scientific strategy.

Participants also pointed out a number of disadvantages of an adaptive network strategy. One scientist characterized some of CPCCRN's activities as "chasing the next dollar", and pointed out that an adaptive strategy would require a great deal of time and effort devoted to grant writing, potentially taking away from a strong research focus. An adaptive strategy is likely to generate less scientific synergy between research projects and limiting economies of scale. An adaptive strategy would require broad expertise on a wide range of topics within the network, which can be difficult to achieve in a program of limited size. Members of the expert panel also stated that CPCCRN – and programs that involve similar approaches – can give the appearance of an insular group that supports members' pet research projects and is not open to outside participation. This appearance can be exacerbated if the projects supported by the network are very diverse, and the network is not presenting to the overall field with an easily-understood, coherent research mission.

The research program evaluation literature, expert panel members, and CPCCRN PIs and Alternate PIs all indicated that performance

measures traditionally used for clinical trials networks may not be appropriate for a network that uses an adaptive strategy. Such networks often involve a greater number of smaller studies, or shorter-term research, that is less likely to yield publication in high-impact journals or immediate changes in clinical practice. Should CPCCRN adopt this type of strategy in setting network priorities, other measures may be more important. Some of these measures were used in this evaluation. These measures could include:

- speed to subject recruitment, and diversity of subjects;
- leveraging of funds;
- new partnerships and collaborations formed;
- time from study initiation to completion;
- follow-on studies, either in the network or elsewhere;
- involvement of new investigators;
- effective communication to the research field;
- citation speed, diversity of journals, and other types of bibliometric measures that emphasize shorter-term impact.

A variety of considerations are appropriate for networks that follow an adaptive research type of model. For example, this approach would require the network to forge strong connections with other funding organizations within and outside the NIH. A strong and well-connected project scientist, one PI suggested, is essential for such a network to thrive. Although traditional strategic planning was not favored, one CPCCRN participant indicated that systematic and frequent portfolio analysis could help identify research gaps and areas where NIH ICs may have special interests. Two expert panel members indicated that communicating the network's strategy to the scientific field and within the NIH is especially important, especially if CPCCRN plans to continue to look for opportunities for outside funding. Others suggested that a framework for outside collaborations would be helpful, and one expert panel member urged CPCCRN to consider a stronger relationship with PALISI. Several panel members and some NICHD project scientists and program officers with other networks sugegsted that although flexibility was certainly desirable, a strong vetting process for research protocols was worthwhile.

Pilot Studies Network

Several of CPCCRN's protocols, including Bereavement, FSS, THAPCA, and CQ, involved pilot studies to set the stage for more definitive studies later on. One PI stated that the nature of CPCCRN was to "Think big, but act incrementally". He stated that large-scale trials are more often successful when strong preliminary data have been obtained, measures are well validated and documented, practice variation accounted for, and a clinical trial is thoroughly planned. A network could concentrate on laying such "groundwork" across the field, leaving the more definitive research to other funding sources. Scientific and strategic planning could be conducted within such a framework, and program goals could be broad or focused.

A pilot studies approach would offer several advantages. It may require fewer resources compared with a clinical trial network or a large-scale observational network, and could offer a key place for younger investigators to gain experience. By developing preliminary data in a rigorous collaborative setting, such a network can make pediatric critical care research attractive to NIH ICs and other funding agencies, as one expert panel member pointed out. This approach would allow for a diversified portfolio in a field with broad needs.

However, this approach also comes with disadvantages. Pilot studies may be less attractive or prestigious to senior investigators, and may be viewed as having more limited scientific payoff. As with an adaptive approach, time and effort must be devoted to grant writing, and the need for strong outside connections is paramount.

As with an adaptive approach, traditional clinical trials measures may be less appropriate if the network is focused on preliminary studies and "seeding" pilot work. Performance measures to consider as alternatives might include:

- subject recruitment, and diversity of subjects;
- leveraging of funds;
- new partnerships and collaborations formed;

- ability to meet requirements for scientific rigor, often imposed by funders for applications to conduct larger trials;
- follow-on studies, either in the network or elsewhere;
- involvement of new investigators; and
- effective communication to the research field, especially for negative findings and for projects that do not move to further stages because a larger trial is determined to be infeasible.

A variety of considerations are appropriate for networks that follow a pilot studies model. For example, this approach would require the network to forge strong connections with other funding organizations within and outside the NIH. If the network developed specialized expertise in meeting the requirements for pilot studies imposed by NIH ICs and other funders, it could provide an essential service to the field. Such a network may need additional mechanisms to help involve young investigators, such as links to K12 and T32 training programs.

Observational Studies Infrastructure

One member of the expert panel suggested that CPCCRN be structured to provide infrastructure for pilot and large-scale observational studies. Such a network would be set up to provide registries and core data services, biospecimen repositories, and modeling, statistical, and research design support to researchers. Projects conducted in such a network could vary in size, scope, and topic.

A network for observational studies may offer several advantages. Several members of the expert panel panel and CPCCRN participants expressed the view that observational studies in the areas of practice variation, quality of care, and implementation science are crucially needed in pediatric critical care, and an observational studies network could create a series of synergistic studies to meet this need. In a field where subject recruitment is challenging and special expertise is needed, a network could be especially important. In addition, one member of the expert panel strongly believed that genetic and genomic research was a urgent

need for the field of pediatric critical care, and a biospecimen repository could greatly facilitate such studies.

An observational studies network also carries with it some disadvantages. There was no clear consensus among CPCCRN participants and expert panel members about what types of research are most needed – one PI stated, "what kind of research do we need? More of everything!". An observational studies network may require a larger initial investment, at least until data systems are established, and this may leave less funding available for intervention research. NICHD staff pointed out that an observational network can present a difficult dilemma for a funding agency in balancing the need to re-compete sites and the value of continuity.

Although publication-based productivity measures would be one way to assess the success of an observational studies network, other measures would also be needed. Data sharing measures, including the availability of public use data, would be very important in assessing such a network. Satisfaction of data users as well as network participants would be also valuable, especially if such measures encompassed both core resources and final data. Moreover, it would be important to trace the development of follow-on intervention studies based on the network's work, quality of care and practice changes, and other longer-term results.

In developing an observational studies network, network participants and NICHD would need to commit to a substantial initial investment. In addition to the infrastructure, network development, and research, resources would be required to launch a communications effort to reach out to the research community to ensure that network resources would be widely and efficiently used. A carefully-aligned set of processes would need to be developed to align incentives for participation and sharing, for researchers both inside and outside the network umbrella. Data sharing issues could be especially challenging, but important, to address.

Clinical Trials Network

The randomized, double-blind, controlled clinical trial has long been viewed by many as a "gold standard" for research, and several CPCCRN PIs and expert panel members wanted to focus on clinical trials in pediatric critical care. These trials may have a high impact on clinical practice. Many clinical trials supported by NIH are conducted within research networks set up specifically for this purpose. NIH-funded clinical trial networks typically rely on a strong scientific planning and review process to identify and design the most important studies to conduct.

Some CPCCRN participants and expert panel members pointed out advantages of a stronger focus on clinical trials. These included the prestige of a clinical trials network, the ability to promote a research culture at participating institutions, and the visibility of such studies. Several CPCCRN participants stated that a stronger focus on clinical trials would help propel the network to a greater leadership role in the field. Proponents of clinical trials also pointed to the network structure as an efficient method for conducting trials at lower cost, compared with conducting trials on a study-by-study basis.

However, other participants felt that a stronger focus on clinical trials would be misplaced at this time. One expert panel member and another CPCCRN participant stated that the field was not read for a focus on clinical trials because the science of pediatric critical care was still underdeveloped. An Alternate PI pointed out that clinical trials often produce inconclusive results in emerging fields like pediatric critical care. Several CPCCRN PI participants pointed to the CRISIS study, conducted in CPCCRN's early years, as a clinical trial which produced a negative result – "an expensive lesson", one participant noted. Scientific risk in clinical trials is high because a great deal of resources, time, and success are centered on a small number of large studies. A large number of subjects are needed and recruitment can be uncertain, especially in a field like pediatric critical care where patient admissions related to specific conditions can be unpredictable.

Clinical trials networks are traditionally assessed using a variety of metrics, including:

- recruitment-based measures;
- publications and bibliometric measures, especially publication in high-impact clinical research journals; and
- changes in clinical practice and practice guidelines.

Should CPCCRN adopt a stronger focus on clinical trials, the network may require a larger investment to field a sufficient number of studies. CPCCRN has addressed this challenge thus far through leveraging of funds because network funds have not been sufficient to support clinical trials. The entire CPCCRN allowance for research protocols, at $1.76M in 2013, is less than the protocol costs for either of the large studies the network is participating in currently. In addition, CPCCRN's current size may be too small to obtain a sufficiently large number of subjects for most research topics. CPCCRN's planning and review processes may also need to be strengthened if the network turns to supporting more clinical trials.

Conclusion

CPCCRN has clearly played an important role in the field of pediatric critical care as a whole, and represents the cornerstone of NICHD's efforts to move the science forward in this area. CPCCRN has demonstrated that rigorous clinical research in pediatric critical care is challenging, but possible. The field faces a series of challenges that encompass the myriad issues faced by clinical reseachers, pediatric researchers, and critical care researchers, all simultaneously. CPCCRN shows that specialized expertise, particularly in critical care nursing and research coordination, is especially important. In considering the future of the network, establishing a strong and clearly-communicated purpose or "identity" could help CPCCRN strengthen its leadership role and also identify the most appropriate performance measures for the network.

Appendix 1: CPCCRN Studies and Protocols: Brief Descriptions

Note: for some items, initial and follow-on studies have been grouped together.

1. Bereavement and Complicated Grief: CPCCRN investigators measured the incidence of complicated grief in bereaved parents at 6 and 18 months, using previously validated survey instruments; evaluated physicians' perspectives on follow-up conferences after the death of a child; developed a structured framework for these meetings; and evaluated the feasibility of using the framework that was developed in a clinical trial to assess the effectiveness of follow-up conferences in preventing complicated grief.

2. Functional Status (FSS and TOPICC): In the Development of a Quantitative Functional Status Scale (FSS) for Pediatric Patients study, CPCCRN investigators tested a new functional status scoring system that had been developed with 500 initial patients and validated with a test set of 250 additional patients. The Trichotomous Outcome Prediction in Critical Care (TOPICC) Study has enrolled more than 10,000 PICU patients and will attempt to predict the outcome of PICU admissions in a trichotomous manner, using the three outcomes of good survival, poor survival, and death. If a predictive model is successfully developed, this model could be used in future studies to assess the quality of care in different intensive care units, and it may also be a useful outcome measure for interventional PICU trials.

3. Opiod Tolerance (MOTIF): The Measuring Opioid Tolerance Induced by Fentanyl (MOTIF) Study was a prospective, observational study designed to estimate the incidence and risk factors for opioid tolerance in critically ill children and describe analgesic practices in the PICU. Significant variability occurred in clinical practices, with up to 100-fold differences in baseline opioid doses, average daily or total doses, or peak infusion rates across PICUs. Between 15 and 20 percent of patients required increased dosage of opiods after 1-2 weeks of therapy.

4. ECMO/BATE: The Bleeding and Thrombosis During ECMO (BATE) Study aims to quantify the incidence of bleeding and thrombosis adverse events in 600 ECMO patients and to explore potential associations of complications with variations in anticoagulation protocols at different hospitals.

5. PEACE(AZ): The Pediatric ECMO and Cefepime (and Zosyn) Study, or PEACE(AZ), is being conducted in conjunction with BATE. PEACE(AZ) aims to enhance the knowledge base regarding the impact of ECMO on cefepime pharmacokinetics to help improve accurate dosing. This study

is also evaluating piperacillin and tazobactam pharmacokinetics in ECMO patients when cefepime is not utilized. These pharmacokinetic data will be important in ECMO patients because therapeutic drug monitoring is not available for these three antibiotics.

6. Critical Asthma: CPCCRN investigators documented large variation between sites in the management of critical asthma, including mechanical ventilation in pediatric patients.

7. Mechanical Ventilation Protocols: Adult ventilator computer protocols have been successful in reducing practice variation in adult critical care. CPCCRN investigators assessed the acceptability of computer support decisions to PICU physicians and nurses.

8. Therapeutic Hypothermia After Pediatric Cardiac Arrest (THAPCA): The THAPCA clinical trials aim to determine whether therapeutic hypothermia, in which the body's temperature is lowered and maintained several degrees below normal for a limited period of time, is as successful at treating children who experience cardiac arrest as it has been in treating adults. The THAPCA project will evaluate therapeutic hypothermia's efficacy at increasing survival rates and reducing the risk of brain injury in infants and children who experience a cardiac arrest while out of the hospital or in the hospital.

9. Hypothermia's Impact on Pharmacology (HIP): This study is an ancillary study to the THAPCA trials. This study will evaluate the metabolism of morphine and midazolam, agents that are commonly used in the critical care setting, within the context of hypothermia.

10. Pediatric Intensive Care Quality of CPR (PICqCPR): The PICqCPR Study is designed to assess whether American Heart Association guidelines for proper performance of cardiopulmonary resuscitation (CPR) are utilized in the hospital setting, particularly within the PICU. This study is evaluating high-fidelity physiological data (arterial waveforms) in PICU patients during CPR. The goal is to identify areas for improving CPR performance in the PICU setting.

11. Critical Pertussis: The Critical Pertussis study is a prospective cohort study to characterize the acute course of critical pertussis in children. Researchers are collecting detailed data on pertussis-related mortality, organ failure, level of support, disability, and the burden for families. Scientists will assess potential associations between acute course characteristics, mortality, and long-term neurobehavioral outcomes for survivors and their families. In addition, CPCCRN researchers are partnering with an NIH basic science laboratory to improve

understanding of the genomic and biological underpinnings of pertussis.

12. Critical Illness Stress-induced Immune Suppression (CRISIS): The CRISIS study assessed "prophylaxis" strategies used to prevent stress-induced nosocomial infection and sepsis. The study used a double-blind, randomized, controlled trial design to test the hypothesis that daily prophylaxis with metoclopramide, zinc, selenium, and glutamine would reduce nosocomial infection and sepsis in critically ill children. The study was terminated for futility after enrollment of 293 subjects.

13. Cortisol Quantification (CQI) study evaluated adrenocortical function in children with sepsis and septic shock. CPCCRN investigators developed and validated an ultracentrifugation method that enables free cortisol quantification within 2 hours. This method will enable rigorous study of adrenocortical function in future studies of pediatric sepsis.

14. LAPSE: The Life After Pediatric Sepsis Evaluation (LAPSE) is a prospective observational study to describe short and long-term outcomes among a cohort of children surviving septic shock. LAPSE will investigate the intensity and duration of persistent sepsis-associated morbidity, through serial measurements of health related quality of life and functional status. In addition LAPSE will examine organ dysfunction, as well as individual and environmental characteristics that may influence these outcome measures.

15. PHENOMS: Inflammation Phenotypes in Pediatric Sepsis Induced Multiple Organ Failure (PHENOMS) is a prospective observational cohort study to enroll 400 children with severe sepsis to test the hypotheses that children with specific sepsis phenotypes have; 1) increased mortality, 2) predisposing genotype and environmental risk factors, and 3) increased CRP and Ferritin levels that correlate with clinical outcome. If patients' clinical outcomes are related to a spectrum of inflammation pathobiology and increased systemic inflammation biomarkers, then phenotype specific therapies directed to normalizing CRP and Ferritin levels may be effective in children with severe sepsis-induced multiple organ failure.

Appendix II: CPCCRN Publications

Collaborative Pediatric Critical Care Research Network (CPCCRN)
Bibliography with Abstracts
2006-2014

Note: not all publications here represent projects of the entire network.

Pollack M.M., Holubkov R., Funai T., Clark A., Moler F., Shanley T., Meert K., Newth C.J.L., Carcillo J., Berger J.T., Doctor A., Berg R.A., Dalton H., Wessel D.L., Harrison R.E., Dean J.M., Jenkins T.L. (2014). Relationship between the functional status scale and the pediatric overall performance category and pediatric cerebral performance category scales, JAMA Pediatrics, 168 (7), 671--676.

IMPORTANCE: Functional status assessment methods are important as outcome measures for pediatric critical care studies. OBJECTIVE: To investigate the relationships between the 2 functional status assessment methods appropriate for large-sample studies, the Functional Status Scale (FSS) and the Pediatric Overall Performance Category and Pediatric Cerebral Performance Category (POPC/PCPC) scales. DESIGN, SETTING, AND PARTICIPANTS: Prospective cohort study with random patient selection at 7 sites and 8 children's hospitals with general/medical and cardiac/cardiovascular pediatric intensive care units (PICUs) in the Collaborative Pediatric Critical Care Research Network. Participants included all PICU patients younger than 18 years. MAIN OUTCOMES AND MEASURES: Functional Status Scale and POPC/PCPC scores determined at PICU admission (baseline) and PICU discharge.We investigated the association between the baseline and PICU discharge POPC/PCPC scores and the baseline and PICU discharge FSS scores, the dispersion of FSS scores within each of the POPC/PCPC ratings, and the relationship between the FSS neurologic components (FSS-CNS) and the PCPC. RESULTS: We included 5017 patients.We found a significant (P < .001) difference between FSS scores in each POPC or PCPC interval, with an FSS score increase with each worsening POPC/PCPC rating. The FSS scores for the good and mild disability POPC/PCPC ratings were similar and increased by 2 to 3 points for the POPC/PCPC change from mild to moderate disability, 5 to 6 points for moderate to severe disability, and 8 to 9 points for severe disability to vegetative state or coma. The dispersion of FSS scores within each POPC and PCPC rating was substantial and increased with worsening POPC and PCPC scores.We also found a significant (P < .001) difference between the FSS-CNS scores between each of the PCPC ratings with increases in the FSS-CNS score for each higher PCPC rating. CONCLUSIONS AND RELEVANCE: The FSS and POPC/PCPC system are closely associated. Increases in FSS scores occur with each higher POPC and PCPC rating and with greater magnitudes of change as the dysfunction severity increases. However, the dispersion of the FSS scores indicated a lack of precision in the POPC/PCPC system when compared with the more objective and granular FSS. The relationship between the PCPC and the FSS-CNS paralleled the relationship between the FSS and POPC/PCPC system.

Topjian A.A., French B., Sutton R.M., Conlon T., Nadkarni V.M., Moler F.W., Dean J.M., Berg R.A. (2014). Early postresuscitation hypotension is associated with increased mortality following pediatric cardiac arrest, Critical Care Medicine, 42 (6), 1518--1523.

OBJECTIVE: To describe the association of systolic hypotension during the first 6 hours after successful resuscitation from pediatric cardiopulmonary arrest with in-hospital mortality. DESIGN: Retrospective cohort study. SETTING: Fifteen children's hospitals associated with the Pediatric Emergency Care Applied Research Network. PATIENTS: Patients between 1 day and 18 years old who had a cardiopulmonary arrest, received chest compressions more than 1 minute, had a return of spontaneous circulation more than 20 minutes, and had a systolic blood pressure documented within 6 hours of arrest. INTERVENTIONS: None. MEASUREMENTS AND MAIN RESULTS: Three hundred eighty-three patients had complete data for analysis. Patients with a documented minimum systolic blood pressure less than fifth percentile for age and sex within the first 6 hours following return of spontaneous circulation were considered to have early postresuscitation hypotension. Two hundred fourteen patients (56%) had early postresuscitation hypotension. One hundred eighty-four patients (48%) died prior to hospital discharge. After controlling for patient and cardiopulmonary arrest characteristics, hypotension in the first 6 hours following return of spontaneous circulation was associated with a significantly increased odds of in-hospital mortality (adjusted odds ratio = 1.71; 95% CI, 1.02-2.89; p = 0.042) and odds of unfavorable outcome (adjusted odds ratio = 1.83; 95% CI, 1.06-3.19; p = 0.032). CONCLUSIONS: In the first 6 hours following successful resuscitation from pediatric cardiac arrest, systolic hypotension was documented in 56% and was associated with a higher rate of in-hospital mortality and worse hospital discharge neurologic outcomes. © 2014 by the Society of Critical Care Medicine and Lippincott Williams & Wilkins.

Anand K.J.S., Clark A.E., Willson D.F., Berger J., Meert K.L., Zimmerman J.J., Harrison R., Carcillo J.A., Newth C.J.L., Bisping S., Holubkov R., Dean J.M., Nicholson C.E. (2013). Opioid analgesia in mechanically ventilated children: Results from the multicenter measuring opioid tolerance induced by fentanyl study*, Pediatric Critical Care Medicine, 14 (1), 27--36.

OBJECTIVE:: To examine the clinical factors associated with increased opioid dose among mechanically ventilated children in the pediatric intensive care unit. DESIGN:: Prospective, observational study with 100% accrual of eligible patients. SETTING:: Seven pediatric intensive care units from tertiary-care children's hospitals in the Collaborative Pediatric Critical Care Research Network. PATIENTS:: Four hundred nineteen children treated with morphine or fentanyl infusions. INTERVENTIONS:: None. MEASUREMENTS AND MAIN RESULTS:: Data on opioid use, concomitant therapy, demographic and explanatory variables were collected. Significant variability occurred in clinical practices, with up to 100-fold differences in baseline opioid doses, average daily or total doses, or peak infusion rates. Opioid exposure for 7 or 14 days required doubling of the daily opioid dose in 16% patients (95% confidence interval 12%-19%) and 20% patients (95% confidence interval 16%-24%), respectively.

Among patients receiving opioids for longer than 3 days (n = 225), this occurred in 28% (95% confidence interval 22%-33%) and 35% (95% confidence interval 29%-41%) by 7 or 14 days, respectively. Doubling of the opioid dose was more likely to occur following opioid infusions for 7 days or longer (odds ratio 7.9, 95% confidence interval 4.3-14.3; p < 0.001) or co-therapy with midazolam (odds ratio 5.6, 95% confidence interval 2.4-12.9; p < 0.001), and it was less likely to occur if morphine was used as the primary opioid (vs. fentanyl) (odds ratio 0.48, 95% confidence interval 0.25-0.92; p = 0.03), for patients receiving higher initial doses (odds ratio 0.96, 95% confidence interval 0.95-0.98; p < 0.001), or if patients had prior pediatric intensive care unit admissions (odds ratio 0.37, 95% confidence interval 0.15-0.89; p = 0.03). CONCLUSIONS:: Mechanically ventilated children require increasing opioid doses, often associated with prolonged opioid exposure or the need for additional sedation. Efforts to reduce prolonged opioid exposure and clinical practice variation may prevent the complications of opioid therapy. Copyright © 2013 by the Society of Critical Care Medicine and the World.

Bell M.J., Kochanek P.M. (2013). Pediatric Traumatic Brain Injury in 2012. The Year with New Guidelines and Common Data Elements., Critical Care Clinics, 29 (2), 223--238.

Traumatic brain injury (TBI) remains the leading cause of death of children in the developing world. In 2012, several international efforts were completed to aid clinicians and researchers in advancing the field of pediatric TBI. The second edition of the Guidelines for the Medical Management of Traumatic Brain Injury in Infants, Children and Adolescents updated those published in 2003. This article highlights the processes involved in developing the Guidelines, contrasts the new guidelines with the previous edition, and delineates new research efforts needed to advance knowledge. The impact of common data elements within these potential new research fields is reviewed. © 2013 Elsevier Inc.

Berg R.A., Sutton R.M., Holubkov R., Nicholson C.E., Dean J.M., Harrison R., Heidemann S., Meert K., Newth C., Moler F., Pollack M., Dalton H., Doctor A., Wessel D., Berger J., Shanley T., Carcillo J., Nadkarni V.M. (2013). Ratio of PICU versus ward cardiopulmonary resuscitation events is increasing, Critical Care Medicine, 41 (10), 2292--2297.

Objectives: The aim of this study was to evaluate the relative frequency of pediatric in-hospital cardiopulmonary resuscitation events occurring in ICUs compared to general wards. We hypothesized that the proportion of pediatric cardiopulmonary resuscitation provided in ICUs versus general wards has increased over the past decade, and this shift is associated with improved resuscitation outcomes. Design: Prospective and observational study. Setting: Total of 315 hospitals in the American Heart Association's Get With The Guidelines-Resuscitation database. Patients: Total of 5,870 pediatric cardiopulmonary resuscitation events between January 1, 2000 and September 14, 2010. Cardiopulmonary resuscitation events were defined as external chest compressions longer than 1 minute. Interventions: None. Measurements and main results: The primary outcome was proportion of total ICU versus general

ward cardiopulmonary resuscitation events over time evaluated by chi-square test for trend. Secondary outcome included return of spontaneous circulation following the cardiopulmonary resuscitation event. Among 5,870 pediatric cardiopulmonary resuscitation events, 5,477 (93.3%) occurred in ICUs compared to 393 (6.7%) in inpatient wards. Over time, significantly more of these cardiopulmonary resuscitation events occurred in the ICU compared to the wards (test for trend: $p < 0.01$), with a prominent shift noted between 2003 and 2004 (2000-2003: 87-91% vs 2004-2010: 94-96%). In a multivariable model controlling for within center variability and other potential confounders, return of spontaneous circulation increased in 2004-2010 compared with 2000-2003 (relative risk, 1.08; 95% CI, 1.03-1.13). Conclusions: In-hospital pediatric cardiopulmonary resuscitation is much more commonly provided in ICUs than in wards, and the proportion has increased significantly over the past decade, with concomitant increases in return of spontaneous circulation.

Berger J.T., Carcillo J.A., Shanley T.P., Wessel D.L., Clark A., Holubkov R., Meert K.L., Newth C.J.L., Berg R.A., Heidemann S., Harrison R., Pollack M., Dalton H., Harvill E., Karanikas A., Liu T., Burr J.S., Doctor A., Dean J.M., Jenkins T.L., Nicholson C.E. (2013). Critical pertussis illness in children: A multicenter prospective cohort study, Pediatric Critical Care Medicine, 14 (4), 356--365.

Objective: Pertussis persists in the United States despite high immunization rates. This report characterizes the presentation and acute course of critical pertussis by quantifying demographic data, laboratory findings, clinical complications, and critical care therapies among children requiring admission to the PICU. Design: Prospective cohort study. Setting: Eight PICUs comprising the Eunice Kennedy Shriver National Institute for Child Health and Human Development Collaborative Pediatric Critical Care Research Network and 17 additional PICUs across the United States. Patients: Eligible patients had laboratory confirmation of pertussis infection, were younger than 18 years old, and died in the PICU or were admitted to the PICU for at least 24 hours between June 2008 and August 2011. Interventions: None. Measurements and main results: A total of 127 patients were identified. Median age was 49 days, and 105 (83%) patients were less than 3 months old. Fifty-five (43%) patients required mechanical ventilation and 12 patients (9.4%) died during initial hospitalization. Pulmonary hypertension was found in 16 patients (12.5%) and was present in 75% of patients who died, compared with 6% of survivors ($p < 0.001$). Median WBC was significantly higher in those requiring mechanical ventilation ($p < 0.001$), those with pulmonary hypertension ($p < 0.001$), and nonsurvivors ($p < 0.001$). Age, sex, and immunization status did not differ between survivors and nonsurvivors. Fourteen patients received leukoreduction therapy (exchange transfusion [12], leukopheresis [1], or both [1]). Survival benefit was not apparent. Conclusions: Pulmonary hypertension may be associated with mortality in pertussis critical illness. Elevated WBC is associated with the need for mechanical ventilation, pulmonary hypertension, and mortality risk. Research is indicated to elucidate how pulmonary hypertension, immune responsiveness, and elevated WBC contribute to morbidity and mortality and whether leukoreduction might be efficacious.

Eggly S., Meert K.L., Berger J., Zimmerman J., Anand K.J.S., Newth C.J.L., Harrison R., Carcillo J., Michael Dean J., Willson D.F., Nicholson C. (2013). Physicians' conceptualization of "closure" as a benefit of physician-parent follow-up meetings after a child's death in the pediatric intensive care unit, Journal of Palliative Care, 29 (2), 69--75.

We examined physicians' conceptualization of closure as a benefit of follow-up meetings with bereaved parents. The frequency of use and the meaning of the word "closure" were analyzed in transcripts of interviews with 67 critical care physicians affiliated with the Collaborative Pediatric Critical Care Research Network. In all, 38 physicians (57 percent) used the word "closure" at least once (median: 2; range: 1 to 7), for a total of 86 times. Physicians indicated that closure is a process or trajectory rather than an achievable goal. They also indicated that parents and physicians can move toward closure by gaining a better understanding of the causes and circumstances of the death and by reconnecting with, or resolving relationships between, parents and health professionals. Physicians suggested that a primary reason to conduct follow-up meetings is that such meetings offer parents and physicians an opportunity to move toward closure. Future research should attempt to determine whether followup meetings reduce the negative effects of bereavement for parents and physicians. © 2013 Institut university de gériatrie de Montréal.

Heidemann S.M., Holubkov R., Meert K.L., Dean J.M., Berger J., Bell M., Anand K.J.S., Zimmerman J., Newth C.J.L., Harrison R., Willson D.F., Nicholson C., Carcillo J. (2013). Baseline serum concentrations of zinc, selenium, and prolactin in critically ill children, Pediatric Critical Care Medicine, 14 (4), e202--e206.

Objectives: To describe serum concentrations of zinc, selenium, and prolactin in critically ill children within 72 hours of PICU admission, and to investigate relationships between these immunomodulators and lymphopenia. Design: An analysis of baseline data collected as part of the multicenter Critical Illness Stress Induced Immune Suppression (CRISIS) Prevention Trial. Setting: PICUs affiliated with the Collaborative Pediatric Critical Care Research Network. Patients: All children enrolled in the CRISIS Prevention Trial that had baseline serum samples available for analysis. Interventions: None. Measurements and main results: Of 293 critically ill children enrolled in the CRISIS Prevention Trial, 284 had baseline serum samples analyzed for prolactin concentration, 280 for zinc concentration, and 278 for selenium concentration within 72 hours of PICU admission. Lymphocyte counts were available for 235 children. Zinc levels ranged from nondetectable (< 0.1 μg/mL) to 2.87 μg/mL (mean 0.46 μg/mL and median 0.44 μg/mL) and were below the normal reference range for 235 (83.9%) children. Selenium levels ranged from 26 to 145 ng/mL (mean 75.4 ng/mL and median 74.5 ng/mL) and were below the normal range for 156 (56.1%) children. Prolactin levels ranged from nondetectable (< 1 ng/mL) to 88 ng/mL (mean 12.2 ng/mL and median 10 ng/mL). Hypoprolactinemia was present in 68 (23.9%) children. Lymphopenia was more likely in children with zinc levels below normal than those with zinc levels within or above the normal

range (82 of 193 [42.5%] vs. 10 of 39 [25.6%], p = 0.0498). Neither selenium nor prolactin concentrations were associated with lymphopenia (p = 1.0 and p = 0.72, respectively). Conclusions: Serum concentrations of zinc, selenium, and prolactin are often low in critically ill children early after PICU admission. Low serum zinc levels are associated with lymphopenia, whereas low selenium and prolactin levels are not. The implications of these findings and the mechanisms by which they occur merit further study. Copyright © 2013 by the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies.

Holubkov R., Casper T.C., Dean J.M., Anand K.J.S., Zimmerman J., Meert K.L., Newth C.J.L., Berger J., Harrison R., Willson D.F., Nicholson C. (2013). The role of the data and safety monitoring board in a clinical trial: The CRISIS study, Pediatric Critical Care Medicine, 14 (4), 374--383.

Objectives: Randomized clinical trials are commonly overseen by a Data and Safety Monitoring Board comprised of experts in medicine, ethics, and biostatistics. Data and Safety Monitoring Board responsibilities include protocol approval, interim review of study enrollment, protocol compliance, safety, and efficacy data. Data and Safety Monitoring Board decisions can affect study design and conduct, as well as reported findings. Researchers must incorporate Data and Safety Monitoring Board oversight into the design, monitoring, and reporting of randomized trials. Design: Case study, narrative review. Methods: The Data and Safety Monitoring Board's role during the comparative pediatric Critical Illness Stress-Induced Immune Suppression (CRISIS) Prevention Trial is described. Findings: The National Institutes of Health-appointed CRISIS Data and Safety Monitoring Board was charged with monitoring sample size adequacy and feasibility, safety with respect to adverse events and 28-day mortality, and efficacy with respect to the primary nosocomial infection/sepsis outcome. The Federal Drug Administration also requested Data and Safety Monitoring Board interim review before opening CRISIS to children below 1 yr of age. The first interim analysis found higher 28-day mortality in one treatment arm. The Data and Safety Monitoring Board maintained trial closure to younger children and requested a second interim data review 6 months later. At this second meeting, mortality was no longer of concern, whereas a weak efficacy trend of lower infection/sepsis rates in one study arm emerged. As over 40% of total patients had been enrolled, the Data and Safety Monitoring Board elected to examine conditional power and unmask treatment arm identities. On finding somewhat greater efficacy in the placebo arm, the Data and Safety Monitoring Board recommended stopping CRISIS due to futility. Conclusions: The design and operating procedures of a multicenter randomized trial must consider a pivotal Data and Safety Monitoring Board role. Maximum study design flexibility must be allowed, and investigators must be prepared for protocol modifications due to interim findings. The Data and Safety Monitoring Board must have sufficient clinical and statistical expertise to assess potential importance of interim treatment differences in the setting of multiple looks at accumulating data with numerous outcomes and subgroups. Copyright © 2013 by the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies.

Moler F.W., Silverstein F.S., Meert K.L., Clark A.E., Holubkov R., Browning B., Slomine B.S., Christensen J.R., Dean J.M. (2013). Rationale, timeline, study design, and protocol overview of the therapeutic hypothermia after pediatric cardiac arrest trials, Pediatric Critical Care Medicine, 14 (7), e304--e315.

Objective: To describe the rationale, timeline, study design, and protocol overview of the Therapeutic Hypothermia after Pediatric Cardiac Arrest trials. Design: Multicenter randomized controlled trials. Setting: Pediatric intensive care and cardiac ICUs in the United States and Canada. Patients: Children from 48 hours to 18 years old, who have return of circulation after cardiac arrest, who meet trial eligibility criteria, and whose guardians provide written consent. Interventions: Therapeutic hypothermia or therapeutic normothermia. Measurements and Main Results: From concept inception in 2002 until trial initiation in 2009, 7 years were required to plan and operationalize the Therapeutic Hypothermia after Pediatric Cardiac Arrest trials. Two National Institute of Child Health and Human Development clinical trial planning grants (R21 and R34) supported feasibility assessment and protocol development. Two clinical research networks, Pediatric Emergency Care Applied Research Network and Collaborative Pediatric Critical Care Research Network, provided infrastructure resources. Two National Heart Lung Blood Institute U01 awards provided funding to conduct separate trials of in-hospital and out-of-hospital cardiac arrest. A pilot vanguard phase that included half the clinical sites began on March 9, 2009, and this was followed by full trial funding through 2015. Conclusions: Over a decade will have been required to plan, design, operationalize, and conduct the Therapeutic Hypothermia after Pediatric Cardiac Arrest trials. Details described in this report, such as participation of clinical research networks and clinical trial planning grants utilization, may be of utility for individuals who are planning investigator-initiated, federally supported clinical trials.

Pemberton V.L., Browning B., Webster A., Dean J.M., Moler F.W. (2013). Therapeutic hypothermia after pediatric cardiac arrest trials: The vanguard phase experience and implications for other trials, Pediatric Critical Care Medicine, 14 (1), 19--26.

OBJECTIVE:: To determine whether an 18-month vanguard phase, in the Therapeutic Hypothermia after Pediatric Cardiac Arrest trials, confirmed study feasibility and patient safety, a prerequisite to continued funding by the sponsor. DESIGN:: Randomized controlled trial. SETTING:: Pediatric intensive care and pediatric cardiac care units in 15 clinical sites in the United States and Canada. PATIENTS:: Children aged 48 hrs to 18 yrs of age, with return of circulation after cardiac arrest. INTERVENTIONS:: Therapeutic hypothermia vs. therapeutic normothermia. MEASUREMENTS AND MAIN RESULTS:: The first 15 of 20 potential sites to obtain Institutional Review Board and subcontract approvals were selected as vanguard sites. Institutional Review Board approvals were obtained 92 days (median, interquartile range 65-114) and subcontracts signed 34 days (interquartile range 20-48) after distribution. Sites screened subjects at 13 days (interquartile range 9-21) and enrolled the first subjects 64 days (interquartile range 13-154) after study launch. The recruitment milestone was reached 4 months ahead of schedule, with no safety concerns identified. Overall recruitment in this ongoing trial remains on target. CONCLUSIONS::

The Therapeutic Hypothermia after Pediatric Cardiac Arrest vanguard phase proved beneficial for the investigators and funding agency. Because complex multicenter trials are rarely ready to launch when grant funds are received, the vanguard allowed time to refine the protocol and recruitment approaches. Competition for vanguard positions led to expedient Institutional Review Board and subcontract completion. Early success and sustained momentum contributed to recruitment at or above goals. Financial risks to the sponsor were minimized by tying funding for the full trial to achieving prespecified milestones. A vanguard phase may be a desirable strategy for the successful conduct of other complex clinical trials.

Pollack M.M., Dean J.M., Butler J., Holubkov R., Doctor A., Meert K.L., Newth C.J., Berg R.A., Moler F., Dalton H., Wessel D.L., Berger J., Harrison R.E., Carcillo J.A., Shanley T.P., Nicholson C.E. (2013). The ideal time interval for critical care severity-of-illness assessment., Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies, 14 (5), 448--453.

Determine if the shortest sampling interval for laboratory variables used to estimate baseline severity of illness in pediatric critical care is equivalently sensitive across multiple sites without site-specific bias, while accounting for the vast majority of dysfunction compared with the standard 0- to 12-hour Pediatric Risk of Mortality III score. Prospective random patient selection. General/medical and cardiac/cardiovascular PICUs in eight hospitals. Patients younger than 18 years admitted to the PICU. None. A total of 376 patients were included. Measurements for Pediatric Risk of Mortality III laboratory variables (pH, PCO2, total CO2, PaO2, glucose, potassium, blood urea nitrogen, creatinine, total WBC count, platelet count, and prothrombin time/partial thromboplastin time) were recorded from 2 hours prior to PICU admission through 12 hours of PICU care except for data in the operating room. Decreasing the observation period from 0 to 12 hours post-PICU admission resulted in progressive decreases in the Pediatric Risk of Mortality III laboratory variables measured. However, allowing the observation period to start 2 hours prior to PICU admission to 4 hours reduced this loss to only 3.4%. Similar trends existed for each of the individual laboratory Pediatric Risk of Mortality III variables. There was a nearly identical distribution of laboratory Pediatric Risk of Mortality III points within the -2- to 4-hour period compared with the standard period. We did not detect any institutional bias using the -2- to 4-hour time period compared with the baseline. Prognostically important laboratory physiologic data collected within the interval from 2 hours prior to PICU to admission through 4 hours after admission account for the vast majority of dysfunction that these variables would contribute to Pediatric Risk of Mortality III scores. There was no institutional bias associated with this sampling period.

Pollack M.M., Dean J.M., Butler J., Holubkov R., Doctor A., Meert K.L., Newth C.L., Berg R.A., Moler F., Dalton H., Wessel D.L., Berger J., Harrison R.E., Carcillo J.A.,

Shanley T.P., Nicholson C.E. (2013). The ideal time interval for critical care severity-of-illness assessment, Pediatric Critical Care Medicine, (), --.

OBJECTIVE:: Determine if the shortest sampling interval for laboratory variables used to estimate baseline severity of illness in pediatric critical care is equivalently sensitive across multiple sites without site-specific bias, while accounting for the vast majority of dysfunction compared with the standard 0- to 12-hour Pediatric Risk of Mortality III score. DESIGN:: Prospective random patient selection. SETTING:: General/medical and cardiac/cardiovascular PICUs in eight hospitals. PATIENTS:: Patients younger than 18 years admitted to the PICU. INTERVENTIONS:: None. MEASUREMENTS AND MAIN RESULTS:: A total of 376 patients were included. Measurements for Pediatric Risk of Mortality III laboratory variables (pH, PCO2, total CO2, PaO2, glucose, potassium, blood urea nitrogen, creatinine, total WBC count, platelet count, and prothrombin time/partial thromboplastin time) were recorded from 2 hours prior to PICU admission through 12 hours of PICU care except for data in the operating room. Decreasing the observation period from the 0 to 12 hours post PICU admission resulted in progressive decreases in the Pediatric Risk of Mortality III laboratory variables measured. However, allowing the observation period to start 2 hours prior to PICU admission to 4 hours reduced this loss to only 3.4%. Similar trends existed for each of the individual laboratory Pediatric Risk of Mortality III variables. There was a nearly identical distribution of laboratory Pediatric Risk of Mortality III points within the -2- to 4-hour period compared with the standard period. We did not detect any institutional bias using the -2- to 4-hour time period compared with the baseline. CONCLUSIONS:: Prognostically important laboratory physiologic data collected within the interval from 2 hours prior to PICU to admission through 4 hours after admission account for the vast majority of dysfunction that these variables would contribute to Pediatric Risk of Mortality III scores. There was no institutional bias associated with this sampling period.

Bratton S.L., Newth C.J.L., Zuppa A.F., Moler F.W., Meert K.L., Berg R.A., Berger J., Wessel D., Pollack M., Harrison R., Carcillo J.A., Shanley T.P., Liu T., Holubkov R., Dean J.M., Nicholson C.E. (2012). Critical care for pediatric asthma: Wide care variability and challenges for study, Pediatric Critical Care Medicine, 13 (4), 407--414.

OBJECTIVES: To describe pediatric severe asthma care, complications, and outcomes to plan for future prospective studies by the Collaborative Pediatric Critical Care Research Network. DESIGN: Retrospective cohort study. SETTING: Pediatric intensive care units in the United States that submit administrative data to the Pediatric Health Information System. PATIENTS: Children 1-18 yrs old treated in a Pediatric Health Information System pediatric intensive care unit for asthma during 2004-2008. INTERVENTIONS: None. MEASUREMENTS AND MAIN RESULTS: Thirteen-thousand five-hundred fifty-two children were studied; 2,812 (21%) were treated in a Collaborative Pediatric Critical Care Research Network and 10,740 (79%) were treated in a non-Collaborative Pediatric Critical Care Research Network pediatric intensive care unit. Medication use in individual Collaborative Pediatric Critical Care Research Network centers differed widely: ipratropium bromide (41%-84%), terbutaline (11%-74%), magnesium sulfate (23%-64%), and methylxanthines (0%-46%). Complications including pneumothorax (0%-0.6%), cardiac arrest (0.2%-2%),

and aspiration (0.2%-2%) were rare. Overall use of medical therapies and complications at Collaborative Pediatric Critical Care Research Network centers were representative of pediatric asthma care at non-Collaborative Pediatric Critical Care Research Network pediatric intensive care units. Median length of pediatric intensive care unit stay at Collaborative Pediatric Critical Care Research Network centers was 1 to 2 days and death was rare (0.1%-3%). Ten percent of children treated at Collaborative Pediatric Critical Care Research Network centers received invasive mechanical ventilation compared to 12% at non-Collaborative Pediatric Critical Care Research Network centers. Overall 44% of patients who received invasive mechanical ventilation were intubated in the pediatric intensive care unit. Children intubated outside the pediatric intensive care unit had significantly shorter median ventilation days (1 vs. 3), pediatric intensive care unit days (2 vs. 4), and hospital days (4 vs. 7) compared to those intubated in the pediatric intensive care unit. Among children who received mechanical respiratory support, significantly more (41% vs. 25%) were treated with noninvasive ventilation and significantly fewer (41% vs. 58%) were intubated before pediatric intensive care unit care when treated in a Pediatric Health Information System hospital emergency department. CONCLUSIONS: Marked variations in medication therapies and mechanical support exist. Death and other complications were rare. More than half of patients treated with mechanical ventilation were intubated before pediatric intensive care unit care. Site of respiratory mechanical support initiation was associated with length of stay.

Carcillo J.A., Dean J.M., Holubkov R., Berger J., Meert K.L., Anand K.J.S., Zimmerman J., Newth C.J.L., Harrison R., Burr J., Willson D.F., Nicholson C. (2012). The randomized comparative pediatric critical illness stress-induced immune suppression (CRISIS) prevention trial, Pediatric Critical Care Medicine, 13 (2), 165--173.

OBJECTIVES: Nosocomial infection/sepsis occurs in up to 40% of children requiring long-term intensive care. Zinc, selenium, glutamine, metoclopramide (a prolactin secretalogue), and/or whey protein supplementation have been effective in reducing infection and sepsis in other populations. We evaluated whether daily nutriceutical supplementation with zinc, selenium, glutamine, and metoclopramide, compared to whey protein, would reduce the occurrence of nosocomial infection/sepsis in this at-risk population. DESIGN: Randomized, double-blinded, comparative effectiveness trial. SETTING: Eight pediatric intensive care units in the National Institutes of Child Health and Human Development Collaborative Pediatric Critical Care Research Network. PATIENTS: Two hundred ninety-three long-term intensive care patients (age 1-17 yrs) expected to require >72 hrs of invasive care. INTERVENTIONS: Patients were stratified according to immunocompromised status and center and then were randomly assigned to receive daily enteral zinc, selenium, glutamine, and intravenous metoclopramide (n = 149), or daily enteral whey protein (n = 144) and intravenous saline for up to 28 days of intensive care unit stay. The primary end point was time to development of nosocomial sepsis/infection. The analysis was intention to treat. MEASUREMENTS AND MAIN RESULTS: There were no differences by assigned treatment in the overall population with respect

to time until the first episode of nosocomial infection/sepsis (median whey protein 13.2 days vs. zinc, selenium, glutamine, and intravenous metoclopramide 12.1 days; p = .29 by log-rank test) or the rate of nosocomial infection/sepsis (4.83/100 days whey protein vs. 4.99/100 days zinc, selenium, glutamine, and intravenous metoclopramide; p = .81). Only 9% of the 293 subjects were immunocompromised and there was a reduction in rate of nosocomial infection/sepsis with zinc, selenium, glutamine, and intravenous metoclopramide in this immunocompromised group (6.09/100 days whey protein vs. 1.57/100 days zinc, selenium, glutamine, and intravenous metoclopramide; p = .011). CONCLUSION: Compared with whey protein supplementation, zinc, selenium, glutamine, and intravenous metoclopramide conferred no advantage in the immune-competent population. Further evaluation of zinc, selenium, glutamine, and intravenous metoclopramide supplementation is warranted in the immunocompromised long-term pediatric intensive care unit patient. Â© 2012 The Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies.

Ghuman A.K., Newth C.J.L., Khemani R.G. (2012). The association between the end tidal alveolar dead space fraction and mortality in pediatric acute hypoxemic respiratory failure, Pediatric Critical Care Medicine, 13 (1), 11--15.

OBJECTIVE:: To investigate the relationship of markers of oxygenation, PaO2/FIO2 ratio, SpO2/FIO2 ratio, oxygenation index, oxygen saturation index, and dead space (end tidal alveolar dead space fraction) with mortality in children with acute hypoxemic respiratory failure. DESIGN:: Retrospective. SETTING:: Single-center tertiary care pediatric intensive care unit. PATIENTS:: Ninety-five mechanically ventilated children with a PaO2/FIO2 ratio <300 within 24 hrs of the initiation of mechanical ventilation. INTERVENTIONS:: None. MAIN RESULTS:: The end tidal alveolar dead space fraction, PaO2/FIO2 ratio, SpO2/FIO2 ratio, oxygenation index, and oxygen saturation index were all associated with mortality (p < .02). There was a small correlation between the end tidal alveolar dead space fraction and decreasing PaO2/FIO2 (r = .21) and SpO2/FIO2 ratios (r = .22), and increasing oxygenation index (r = .25) and oxygen saturation index (r = .24). In multivariate logistic regression modeling, the end tidal alveolar dead space fraction was independently associated with mortality (p < .02). Oxygenation index, oxygen saturation index, and the end tidal alveolar dead space fraction were all acceptable discriminators of mortality with receiver operating characteristic plot area under the curves â‰¥0.7. CONCLUSIONS:: In pediatric acute hypoxemic respiratory failure, easily obtainable pulmonary specific markers of disease severity (SpO2/FIO2 ratio, oxygen saturation index, and the end tidal alveolar dead space fraction) may be useful for the early identification of children at high risk of death. Furthermore, the end tidal alveolar dead space fraction should be considered for risk stratification of children with acute hypoxemic respiratory failure, given that it was independently associated with mortality. Â© 2012 by the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies.

Newth C.J.L., Meert K.L., Clark A.E., Moler F.W., Zuppa A.F., Berg R.A., Pollack M.M., Sward K.A., Berger J.T., Wessel D.L., Harrison R.E., Reardon J., Carcillo J.A., Shanley T.P., Holubkov R., Dean J.M., Doctor A., Nicholson C.E. (2012). Fatal and near-fatal asthma in children: The critical care perspective, Journal of Pediatrics, 161 (2), 214--2.21E+05.

Objective: To characterize the clinical course, therapies, and outcomes of children with fatal and near-fatal asthma admitted to pediatric intensive care units (PICUs). Study design: This was a retrospective chart abstraction across the 8 tertiary care PICUs of the Collaborative Pediatric Critical Care Research Network (CPCCRN). Inclusion criteria were children (aged 1-18 years) admitted between 2005 and 2009 (inclusive) for asthma who received ventilation (near-fatal) or died (fatal). Data collected included medications, ventilator strategies, concomitant therapies, demographic information, and risk variables. Results: Of the 261 eligible children, 33 (13%) had no previous history of asthma, 218 (84%) survived with no known complications, and 32 (12%) had complications. Eleven (4%) died, 10 of whom had experienced cardiac arrest before admission. Patients intubated outside the PICU had a shorter duration of ventilation (median, 25 hours vs 84 hours; P <.001). African-Americans were disproportionately represented among the intubated children and had a shorter duration of intubation. Barotrauma occurred in 15 children (6%) before admission. Pharmacologic therapy was highly variable, with similar outcomes. Conclusion: Of the children ventilated in the CPCCRN PICUs, 96% survived to hospital discharge. Most of the children who died experienced cardiac arrest before admission. Intubation outside the PICU was correlated with shorter duration of ventilation. Complications of barotrauma and neuromyopathy were uncommon. Practice patterns varied widely among the CPCCRN sites. Copyright Ã© 2012 Mosby Inc.

Au A.K., Carcillo J.A., Clark R.S.B., Bell M.J. (2011). Brain injuries and neurological system failure are the most common proximate causes of death in children admitted to a pediatric intensive care unit, Pediatric Critical Care Medicine, 12 (5), 566--571.

Objective: Mortality rates from critical illness in children have declined over the past several decades, now averaging between 2% and 5% in most pediatric intensive care units. Although these rates, and mortality rates from specific disorders, are widely understood, the impact of acute neurologic injuries in such children who die and the role of these injuries in the cause of death are not well understood. We hypothesized that neurologic injuries are an important cause of death in children. Design: Retrospective review. Setting: Pediatric intensive care unit at Children's Hospital of Pittsburgh, an academic tertiary care center. Patients: Seventy-eight children who died within the pediatric intensive care unit from April 2006 to February 2008. Interventions: None. Measurements and Main Results: Data regarding admission diagnosis, presence of chronic illness, diagnosis of brain injury, and cause of death were collected. Mortality was attributed to brain injury in 65.4% (51 of 78) of deaths. Ninety-six percent (28 of 29) of previously healthy children died with brain injuries compared with 46.9% (23 of 49) of chronically ill children (p > .05). The diagnosed brain injury was the proximate cause of death in 89.3% of previously healthy children and 91.3% with chronic illnesses. Pediatric intensive care unit and hospital length of stay was longer in those with chronic illnesses (38.8 

7.0 days vs. 8.9 ┬▒ 3.7 days and 49.2 ┬▒ 8.3 days vs. 9.0 ┬▒ 3.8 days, p > .05 and p > .001, respectively). Conclusion: Brain injury was exceedingly common in children who died in our pediatric intensive care unit and was the proximate cause of death in a large majority of cases. Neuroprotective measures for a wide variety of admission diagnoses and initiatives directed to prevention or treatment of brain injury are likely to attain further improvements in mortality in previously healthy children in the modern pediatric intensive care unit. Copyright ┬⌐ 2011 by the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies.

Eggly S., Meert K.L., Berger J., Zimmerman J., Anand K.J.S., Newth C.J.L., Harrison R., Carcillo J., Dean J.M., Willson D.F., Nicholson C. (2011). A framework for conducting follow-up meetings with parents after a child's death in the pediatric intensive care unit, Pediatric Critical Care Medicine, 12 (2), 147--152.

Objective: To describe a framework to assist pediatric intensive care unit physicians in conducting follow-up meetings with parents after their child's death. Many childhood deaths occur in pediatric intensive care units. Parents of children who die in pediatric intensive care units often desire a follow-up meeting with the physician(s) who cared for their child. Data Sources: Prior research conducted by the Collaborative Pediatric Critical Care Research Network on the experiences and perspectives of bereaved parents and pediatric intensive care unit physicians regarding the desirability, content, and conditions of follow-up meetings. Results: The framework includes suggestions for inviting families to follow-up meetings (i.e., developing an institutional system, invitation timing, and format); preparing for the meeting (i.e., assessing family preferences; determining location, attendees, and discussion topics; reviewing medical and psychosocial history); structure of the meeting (i.e., opening, closing, and developing a meeting agenda); communicating effectively during the meeting; and follow-up for both parents and physicians. Conclusion: This framework is based on the experience and perspectives of bereaved parents and pediatric intensive care unit physicians. Future research should be conducted to determine the extent to which physician-parent follow-up meetings provide a benefit to parents, families, physicians, and other healthcare providers participating in these encounters. Copyright ┬⌐ 2011 by the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies.

Khemani R.G., Sward K., Morris A., Dean J.M., Newth C.J.L. (2011). Variability in usual care mechanical ventilation for pediatric acute lung injury: The potential benefit of a lung protective computer protocol, Intensive Care Medicine, 37 (11), 1840--1848.

Purpose: Although pediatric intensivists claim to embrace lung protective ventilation for acute lung injury (ALI), ventilator management is variable. We describe ventilator changes clinicians made for children with hypoxemic respiratory failure, and evaluate the potential acceptability of a pediatric ventilation protocol. Methods: This was a retrospective cohort study performed in a tertiary care pediatric intensive care unit (PICU). The study period was from January 2000 to July 2007. We included mechanically ventilated children with PaO

2/FiO
2 (P/F) ratio less than 300. We assessed variability in ventilator management by evaluating actual changes to ventilator settings after an arterial blood gas (ABG). We evaluated the potential acceptability of a pediatric mechanical ventilation protocol we adapted from National Institutes of Health/National Heart, Lung, and Blood Institute (NIH/NHLBI) Acute Respiratory Distress Syndrome (ARDS) Network protocols by comparing actual practice changes in ventilator settings to changes that would have been recommended by the protocol. Results: A total of 2,719 ABGs from 402 patients were associated with 6,017 ventilator settings. Clinicians infrequently decreased FiO
2, even when the PaO
2 was high (>68 mmHg). The protocol would have recommended more positive end expiratory pressure (PEEP) than was used in actual practice 42% of the time in the mid PaO
2 range (55-68 mmHg) and 67% of the time in the low PaO
2 range (<55 mmHg). Clinicians often made no change to either peak inspiratory pressure (PIP) or ventilator rate (VR) when the protocol would have recommended a change, even when the pH was greater than 7.45 with PIP at least 35 cmH
2O. Conclusions: There may be lost opportunities to minimize potentially injurious ventilator settings for children with ALI. A reproducible pediatric mechanical ventilation protocol could prompt clinicians to make ventilator changes that are consistent with lung protective ventilation. ┬⌐ 2011 Copyright jointly held by Springer and ESICM.

Meert K.L., Eggly S., Berger J., Zimmerman J., Anand K.J.S., Newth C.J.L., Harrison R., Carcillo J., Dean J.M., Willson D.F., Nicholson C. (2011). Physicians' experiences and perspectives regarding follow-up meetings with parents after a child's death in the pediatric intensive care unit, Pediatric Critical Care Medicine, 12 (2), e64--e68.

Objective: To investigate critical care physicians' experiences and perspectives regarding follow-up meetings with parents after a child's death in the pediatric intensive care unit. Parents of children who die in the pediatric intensive care unit often desire a follow-up meeting with the physicians who cared for their child. Design: Semistructured, audio-recorded telephone interviews. Setting: Six clinical centers affiliated with the Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network. Participants: Seventy critical care physicians (i.e., attendings and fellows) practicing or training at a Child Health and Human Development Collaborative Pediatric Critical Care Research Network clinical center between February 1, 2008 and June 30, 2008. Measurements And Main Results: Twenty-three (33%) physicians reported never participating in a follow-up meeting with bereaved parents; 22 (31%) participated in one to five meetings; and 25 (36%) participated in more than five meetings. Of those with prior experience, 44 (94%) met with parents at the hospital and 40 (85%) met within 3 months of the death. Meeting content included discussing autopsy, parent questions, hospital course, cause of death, genetic risk, bereavement services, and legal or administrative issues; providing emotional support; and receiving parent feedback. Forty (85%) physicians perceived the meetings to be

beneficial to families, and 35 (74%) to physicians. Barriers included time and scheduling, family and physician unwillingness, distance and transportation, language and cultural issues, parent anger, and lack of a system for meeting initiation and planning. Conclusions: Critical care physicians have a wide range of experience conducting follow-up meetings with bereaved parents. Although physicians perceive benefits to follow-up meetings, barriers exist that interfere with their implementation in clinical practice. Copyright ┬⌐ 2011 by the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies.

Meert K.L., Shear K., Newth C.J.L., Harrison R., Berger J., Zimmerman J., Anand K.J.S., Carcillo J., Donaldson A.E., Dean J.M., Willson D.F., Nicholson C. (2011). Follow-up study of complicated grief among parents eighteen months after a child's death in the pediatric intensive care unit, Journal of Palliative Medicine, 14 (2), 207--214.

Objective: We previously demonstrated that parents whose children die in a pediatric intensive care unit (PICU) have a high level of complicated grief symptoms 6 months after the death. In this study, we investigate the change in the extent of complicated grief symptoms among these parents between 6 and 18 months postdeath and identify factors predicting improvement. Methods: One hundred thirty-eight parents of 106 children completed surveys at 6 and 18 months. Surveys included the Inventory of Complicated Grief (ICG), measures of grief avoidance, attachment, caregiving and social support, and demographics. Multivariable analysis was performed using generalized estimating equations to identify characteristics independently associated with improvement in ICG score. Results: ICG scores were 33.4 ┬▒ 13.6 at 6 months and 28.0 ┬▒ 13.5 at 18 months, representing an improvement in ICG score of 5.4 + 8.0 (95% confidence interval [CI] 4.1-6.8, p < 0.001). Variables independently associated with greater improvement in ICG score included traumatic death and greater grief avoidance. Variables independently associated with less improvement included being the biological parent and having more responsive caregiving. Parents with one or two surviving children had more improvement in ICG score than those with no surviving children whereas parents with three or more surviving children had less improvement. Conclusion: Complicated grief symptoms decrease among parents between 6 and 18 months after their child's death in the PICU; however, high symptom levels persists for some. Better understanding of the trajectory of complicated grief will allow parents at risk for persistent distress to receive professional support. ┬⌐ Copyright 2011, Mary Ann Liebert, Inc.

Moler F.W., Donaldson A.E., Meert K., Brilli R.J., Nadkarni V., Shaffner D.H., Schleien C.L., Clark R.S.B., Dalton H.J., Statler K., Tieves K.S., Hackbarth R., Pretzlaff R., Van Der Jagt E.W., Pineda J., Hernan L., Dean J.M. (2011). Multicenter cohort study of out-of-hospital pediatric cardiac arrest, Critical Care Medicine, 39 (1), 141--149.

Objectives: To describe a large cohort of children with out-of-hospital cardiac arrest with return of circulation and to identify factors in the early postarrest period associated with survival. These objectives were for planning an interventional trial of therapeutic hypothermia after pediatric cardiac arrest.

Methods: A retrospective cohort study was conducted at 15 Pediatric Emergency Care Applied Research Network clinical sites over an 18-month study period. All children from 1 day (24 hrs) to 18 yrs of age with out-of-hospital cardiac arrest and a history of at least 1 min of chest compressions with return of circulation for at least 20 mins were eligible. Measurements and main results: One hundred thirty-eight cases met study entry criteria; the overall mortality was 62% (85 of 138 cases). The event characteristics associated with increased survival were as follows: weekend arrests, cardiopulmonary resuscitation not ongoing at hospital arrival, arrest rhythm not asystole, no atropine or NaHCO

3, fewer epinephrine doses, shorter duration of cardiopulmonary resuscitation, and drowning or asphyxial arrest event. For the 0- to 12-hr postarrest return-of-circulation period, absence of any vasopressor or inotropic agent (dopamine, epinephrine) use, higher lowest temperature recorded, greater lowest pH, lower lactate, lower maximum glucose, and normal pupillary responses were all associated with survival. A multivariate logistic model of variables available at the time of arrest, which controlled for gender, age, race, and asystole or ventricular fibrillation/ventricular tachycardia anytime during the arrest, found the administration of atropine and epinephrine to be associated with mortality. A second model using additional information available up to 12 hrs after return of circulation found 1) preexisting lung or airway disease; 2) an etiology of arrest drowning or asphyxia; 3) higher pH, and 4) bilateral reactive pupils to be associated with lower mortality. Receiving more than three doses of epinephrine was associated with poor outcome in 96% (44 of 46) of cases. Conclusions: Multiple factors were identified as associated with survival after out-of-hospital pediatric cardiac arrest with the return of circulation. Additional information available within a few hours after the return of circulation may diminish outcome associations of factors available at earlier times in regression models. These factors should be considered in the design of future interventional trials aimed to improve outcome after pediatric cardiac arrest. Copyright Â© 2010 by the Society of Critical Care Medicine and Lippincott Williams & Wilkins.

Ross P.A., Newth C.J.L. (2011). If the tube fits?, Pediatric Critical Care Medicine, 12 (1), 117--118.

[No abstract available]

Zimmerman J.J., Donaldson A., Barker R.M., Meert K.L., Harrison R., Carcillo J.A., Anand K.J.S., Newth C.J.L., Berger J., Willson D.F., Jack R., Nicholson C., Michael Dean J. (2011). Real-time free cortisol quantification among critically ill children, Pediatric Critical Care Medicine, 12 (5), 525--531.

Objectives: Ascertainment of adrenal function assessing free rather that total cortisol may be beneficial for the diagnosis of critical illness-related cortisol insufficiency. We hypothesized that centrifugal ultrafiltration would provide timely free cortisol data that highly correlated with the gold standard, but logistically cumbersome, equilibrium dialysis technique when the free cortisol fractions were identically quantified by chemiluminescence immunoassay. We also hypothesized that free cortisol would correlate with illness severity in a

large cohort of critically ill children. Design: Prospective, multi-institutional, observational cohort investigation. Setting: Seven pediatric intensive care units within the Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network. Patients: One hundred sixty-five critically ill children across the spectrum of illness severity. Interventions: Blood sampling. Measurements and Main Results: Time to derive plasma free cortisol concentrations after centrifugal ultrafiltration or equilibrium dialysis fractionation with chemiluminescence immunoassay was approximately 2 vs. approximately 24 hrs, respectively. Using centrifugal ultrafiltration, mean plasma free cortisol was 4.1 ┬▒ 6.7 ╬╝g/dL (median, 1.6 ╬╝g/dL; range, 0.2- 43.6 ╬╝g/L), representing an average of 15.2 ┬▒ 9.4% of total cortisol. Nearly 60% of subjects exhibited free cortisol <2 and 30% <0.8 ╬╝g/dL, previously suggested threshold concentrations for defining critical illness-related cortisol insufficiency. Plasma-free cortisol concentrations comparing centrifugal ultrafiltration vs. equilibrium dialysis fractionation demonstrated a strong correlation (R 2 = 0.97). For free cortisol <2 ╬╝g/dL, Bland-Altman analysis revealed minimal negative bias for the centrifugal ultrafiltration technique. Illness severity assessed by Pediatric Risk of Mortality III correlated moderately with free cortisol and percent total cortisol as free cortisol. Conclusions: Determination of centrifugal ultrafiltration fractionated free cortisol was fast and results correlated highly with equilibrium dialysis fractionated free cortisol. Many children exhibited free cortisol <2 and <0.8 ╬╝g/dL but did not demonstrate clinical evidence of critical illness-related cortisol insufficiency. This study ascertains that real-time free cortisol quantification is feasible to potentially help guide clinical decisionmaking for cortisol replacement therapy in the pediatric intensive care unit. Copyright ┬⌐ 2011 by the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies.

Anand K.J.S., Willson D.F., Berger J., Harrison R., Meert K.L., Zimmerman J., Carcillo J., Newth C.J.L., Prodhan P., Dean J.M., Nicholson C. (2010). Tolerance and withdrawal from prolonged opioid use in critically III children, Pediatrics, 125 (5), --.

OBJECTIVE: After prolonged opioid exposure, children develop opioid-induced hyperalgesia, tolerance, and withdrawal. Strategies for prevention and management should be based on the mechanisms of opioid tolerance and withdrawal. PATIENTS AND METHODS: Relevant manuscripts published in the English language were searched in Medline by using search terms "opioid," "opiate," "sedation," "analgesia," "child," "infant-newborn," "tolerance," "dependency," "withdrawal," "analgesic," "receptor," and "individual opioid drugs." Clinical and preclinical studies were reviewed for data synthesis. RESULTS: Mechanisms of opioid-induced hyperalgesia and tolerance suggest important drug - and patient-related risk factors that lead to tolerance and withdrawal. Opioid tolerance occurs earlier in the younger age groups, develops commonly during critical illness, and results more frequently from prolonged intravenous infusions of short-acting opioids. Treatment options include slowly tapering opioid doses, switching to longer-acting opioids, or specifically treating the symptoms of opioid withdrawal. Novel therapies may also include blocking the mechanisms of opioid tolerance, which would enhance the safety and

effectiveness of opioid analgesia. CONCLUSIONS: Opioid tolerance and withdrawal occur frequently in critically ill children. Novel insights into opioid receptor physiology and cellular biochemical changes will inform scientific approaches for the use of opioid analgesia and the prevention of opioid tolerance and withdrawal. Copyright Â© 2010 by the American Academy of Pediatrics.

Anand K.J.S., Willson D.F., Berger J., Harrison R., Meert K.L., Zimmerman J., Carcillo J., Newth C.J.L., Prodhan P., Dean J.M., Nicholson C. (2010). Tolerance and withdrawal from prolonged opioid use in critically III children, Pediatrics, 125 (5), e1208--e1225.

OBJECTIVE: After prolonged opioid exposure, children develop opioid-induced hyperalgesia, tolerance, and withdrawal. Strategies for prevention and management should be based on the mechanisms of opioid tolerance and withdrawal. PATIENTS AND METHODS: Relevant manuscripts published in the English language were searched in Medline by using search terms "opioid," "opiate," "sedation," "analgesia," "child," "infant-newborn," "tolerance," "dependency," "withdrawal," "analgesic," "receptor," and "individual opioid drugs." Clinical and preclinical studies were reviewed for data synthesis. RESULTS: Mechanisms of opioid-induced hyperalgesia and tolerance suggest important drug - and patient-related risk factors that lead to tolerance and withdrawal. Opioid tolerance occurs earlier in the younger age groups, develops commonly during critical illness, and results more frequently from prolonged intravenous infusions of short-acting opioids. Treatment options include slowly tapering opioid doses, switching to longer-acting opioids, or specifically treating the symptoms of opioid withdrawal. Novel therapies may also include blocking the mechanisms of opioid tolerance, which would enhance the safety and effectiveness of opioid analgesia. CONCLUSIONS: Opioid tolerance and withdrawal occur frequently in critically ill children. Novel insights into opioid receptor physiology and cellular biochemical changes will inform scientific approaches for the use of opioid analgesia and the prevention of opioid tolerance and withdrawal. Copyright ┬⌐ 2010 by the American Academy of Pediatrics.

Khemani R.G., Newth C.J.L. (2010). The design of future pediatric mechanical ventilation trials for acute lung injury, American Journal of Respiratory and Critical Care Medicine, 182 (12), 1465--1474.

Pediatric practitioners face unique challenges when attempting to translate or adapt adult-derived evidence regarding ventilation practices for acute lung injury or acute respiratory distress syndrome into pediatric practice. Fortunately or unfortunately, there appears to be selective adoption of adult practices for pediatric mechanical ventilation, many of which pose considerable challenges or uncertainty when translated to pediatrics. These differences, combined with heterogeneous management strategies within pediatric critical care, can complicate clinical practice and make designing robust clinical trials in pediatric acute respiratory failure particularly difficult. These issues surround the lack of explicit ventilator protocols in pediatrics, either computer or paper based; differences in modes of conventional ventilation and perceived

marked differences in the approach to high-frequency oscillatory ventilation; challenges with patient recruitment; the shortcomings of the definition of acute lung injury and acute respiratory distress syndrome; the more reliable yet still somewhat unpredictable relationship between lung injury severity and outcome; and the reliance on potentially biased surrogate outcome measures, such as ventilator-free days, for all pediatric trials. The purpose of this review is to highlight these challenges, discuss pertinent work that has begun to address them, and propose potential solutions or future investigations that may help facilitate comprehensive trials on pediatric mechanical ventilation and define clinical practice standards.

Meert K.L., Donaldson A.E., Newth C.J.L., Harrison R., Berger J., Zimmerman J., Anand K.J.S., Carcillo J., Dean J.M., Willson D.F., Nicholson C., Shear K. (2010). Complicated grief and associated risk factors among parents following a child's death in the pediatric intensive care unit, Archives of Pediatrics and Adolescent Medicine, 164 (11), 1045--1051.

Objective: To investigate the extent of complicated grief symptoms and associated risk factors among parents whose child died in a pediatric intensive care unit. Design: Cross-sectional survey conducted by mail and telephone. Setting: Seven children's hospitals affiliated with the Collaborative Pediatric Critical Care Research Network from January 1, 2006, to June 30, 2008. Participants: Two hundred sixty-one parents from 872 families whose child died in a pediatric intensive care unit 6 months earlier. Main Exposure: Assessment of potential risk factors, including demographic and clinical variables, and parent psychosocial characteristics, such as attachment style, caregiving style, grief avoidance, and social support. Main Outcome Measure: Parent report of complicated grief symptoms using the Inventory of Complicated Grief. Total scale range is from 0 to 76; scores of 30 or higher suggest complicated grief. Results: Mean (SD) Inventory of Complicated Grief scores amongparents were 33.7 (14.1). Fifty-nine percent of parents (95% confidence interval, 53%-65%) had scores of 30orhigher. Variables independently associated with higher symptom scores in multivariable analysis included being the biological mother or female guardian, trauma as the cause of death, greater attachment-related anxiety and attachment-related avoidance, and greater grief avoidance. Conclusions: Parents who responded to our survey experienced a high level of complicated grief symptoms 6 months after their child's death in the pediatric intensive care unit. However, our estimate of the extent of complicated grief symptoms may be biased because of a high number of nonresponders. Better understanding of complicated grief and its risk factors among parents will allow those most vulnerable to receive professional bereavement support. ┬-2010 American Medical Association. All rights reserved.

Willson D.F., Dean J.M., Meert K.L., Newth C.J.L., Anand K.J.S., Berger J., Harrison R., Zimmerman J., Carcillo J., Pollack M., Holubkov R., Jenkins T.L., Nicholson C. (2010). Collaborative pediatric critical care research network: Looking back and moving forward, Pediatric Critical Care Medicine, 11 (1), --.

Objective: To update the pediatric critical care community on the progress of the Collaborative Pediatric Critical Care Research Network and plans for the

future. Setting: The six sites, seven hospitals of the Collaborative Pediatric Critical Care Research Network. Results: From the time of its inception in August 2005, the Network has engaged in a number of observational and interventional trials, several of which are ongoing. Additional studies are in the planning stages. To date, these studies have resulted in the publication of six manuscripts and five abstracts, with five additional manuscripts accepted and in press. Conclusion: The Network remains committed to its stated goal "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. Â© 2010 by the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies.

Willson D.F., Dean J.M., Meert K.L., Newth C.J.L., Anand K.J.S., Berger J., Harrison R., Zimmerman J., Carcillo J., Pollack M., Holubkov R., Jenkins T.L., Nicholson C. (2010). Collaborative pediatric critical care research network: Looking back and moving forward, Pediatric Critical Care Medicine, 11 (1), 1--6+164+165+166.

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Bergqvist L.L., Katz-Salamon M., Hertegard S., Anand K.J.S., Lagercrantz H. (2009). Mode of delivery modulates physiological and behavioral responses to neonatal pain, Journal of Perinatology, 29 (1), 44--50.

Objective: To study whether the mode of delivery alters pain expression. Study Design: Full-term infants born by vaginal delivery or elective caesarean section were observed following high- and low-intensity pain stimuli, with recording of electrocardiogram, facial expression and vocalization. Result: Graded physiological and behavioral responses occurred, with greater responses to higher than lower intensity pain stimuli. Elevation in heart rate following both stimuli increased with time after vaginal delivery. Infants delivered by elective caesarean section showed stronger facial expressions and briefer time in vocalizations response to both interventions. Conclusion: Diminished responses following vaginal delivery suggest that physiological events associated with a normal delivery reduce the physiologic and sympathoadrenal activation by nociceptive mechanisms. Pain and stress reactivity appear to be inhibited during fetal life and sensory inputs during vaginal delivery may reverse this

inhibition. To minimize neonatal pain, we recommend that postnatal invasive procedures to be performed shortly after vaginal birth.

Carcillo J., Holubkov R., Dean J.M., Berger J., Meert K.L., Anand K.J.S., Zimmerman J., Newth C.J.L., Harrison R., Willson D.F., Nicholson C. (2009). Rationale and design of the pediatric critical illness stress-induced immune suppression (CRISIS) prevention trial, Journal of Parenteral and Enteral Nutrition, 33 (4), 368--374.

Despite implementation of CDC recommendations and bundled interventions for preventing catheter-associated blood stream infection, ventilator-associated pneumonia, or urinary catheter-associated infections, nosocomial infections and sepsis remain a significant cause of morbidity and mortality in critically ill children. Recent studies suggest that acquired critical illness stress-induced immune suppression (CRISIS) plays a role in the development of nosocomial infection and sepsis. This condition can be related to inadequate zinc, selenium, and glutamine levels, as well as hypoprolactinemia, leading to stress-induced lymphopenia, a predominant TH2 monocyte/macrophage state, and subsequent immune suppression. Prolonged immune dysfunction increases the likelihood of nosocomial infections associated with invasive devices. Although strategies to prevent common complications of critical illness are routinely employed (eg, prophylaxis for gastrointestinal bleeding, thrombophlebitis), no prophylactic strategy is used to prevent stress-induced immune suppression. This is the authors' rationale for the pediatric CRISIS prevention trial (NCT00395161), designed as a randomized, double-blind, controlled clinical investigation to determine if daily enteral supplementation with zinc, selenium, and glutamine as well as parenteral metoclopramide (a dopamine 2 receptor antagonist that reverses hypoprolactinemia) prolongs the time until onset of nosocomial infection or sepsis in critically ill children compared to enteral supplementation with whey protein. If effective, this combined nutritional and pharmacologic approach may lessen the excess morbidity and mortality as well as resource utilization associated with nosocomial infections and sepsis in this population. The authors present the design and analytic plan for the CRISIS prevention trial. Â© 2009 American Society for Parenteral and Enteral Nutrition.

Holubkov R., Dean J.M., Berger J., Anand K.J.S., Carcillo J., Meert K., Zimmerman J., Newth C., Harrison R., Willson D.F., Nicholson C. (2009). Is "rescue" therapy ethical in randomized controlled trials?, Pediatric Critical Care Medicine, 10 (4), --.

Objective: There is a commonly held belief that randomized, placebo-controlled trials in pediatric critical care should incorporate "rescue" therapy (open-label administration of active drug) when a child's condition is deteriorating. The ethical, conceptual, and analytic challenges related to rescue therapy in randomized trials can be misrepresented. Design: Narrative review. Methods: The ethical basis of rescue therapy, the equipoise concept, and intention-to-treat analysis are examined in the setting of a hypothetical randomized trial comparing corticosteroids vs. placebo in pediatric septic shock. Findings: The perceived need for rescue therapy may be partly motivated by the moral imperative to save a child's life. However, allowing rescue therapy in a trial is misconceived and inconsistent with equipoise regarding the efficacy of the study drug. If rescue therapy is permitted, intention-to-treat analysis can only

compare immediate vs. delayed use of the study drug. When rescue therapy is beneficial, the observed treatment effect is substantially diminished from true effect of the study drug, leading to increased sample size and thereby placing more children at risk (18 "excess" placebo-arm deaths occur in our hypothetical example). Analysis of a trial incorporating rescue therapy cannot definitively assess overall efficacy of the agent, or distinguish beneficial or harmful treatment effects related to timing of drug use. Conclusions: Although a rescue therapy component in a randomized trial may be perceived as ethically desirable, inconsistency of rescue therapy with full equipoise may itself raise significant ethical concerns. Increased sample sizes expose more children to the risks of study participation, including death. Researchers should be aware that clinical trials designed with rescue therapy cannot definitively determine the beneficial or harmful effects of a treatment per se, and can only assess the effects of delayed vs. immediate provision of the treatment. Â© 2009 by the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies.

Khemani R.G., Conti D., Alonzo T.A., Bart III R.D., Newth C.J.L. (2009). Effect of tidal volume in children with acute hypoxemic respiratory failure, Intensive Care Medicine, 35 (8), 1428--1437.

Objectives: To determine if tidal volume (V _T) between 6 and 10 ml/kg body weight using pressure control ventilation affects outcome for children with acute hypoxemic respiratory failure (AHRF) or acute lung injury (ALI). To validate lung injury severity markers such as oxygenation index (OI), PaO₂/FiO₂ (PF) ratio, and lung injury score (LIS). Design: Retrospective, January 2000-July 2007. Setting: Tertiary care, 20-bed PICU. Patients: Three hundred and ninety-eight endotracheally intubated and mechanically ventilated children with PF ratio <300. Outcomes were mortality and 28-day ventilator free days. Measurements and main results: Three hundred and ninety-eight children met study criteria, with 20% mortality. 192 children had ALI. Using >90% pressure control ventilation, 85% of patients achieved V _T less than 10 ml/kg. Median V _T was not significantly different between survivors and non-survivors during the first 3 days of mechanical ventilation. After controlling for diagnostic category, age, delta P (PIP-PEEP), PEEP, and severity of lung disease, V _T was not associated with mortality (P > 0.1), but higher V _T at baseline and on day 1 of mechanical ventilation was associated with more ventilator free days (P < 0.05). This was particularly seen in patients with better respiratory system compliance [Crs > 0.5 ml/cmH₂0/kg, OR = 0.70 (0.52, 0.95)]. OI, PF ratio, and LIS were all associated with mortality (P < 0.05). Conclusions: When ventilating children using lung protective strategies with pressure control ventilation, observed V _T is between 6 and 10 ml/kg and is not associated with increased mortality. Moreover, higher V _T within this range is associated with more ventilator free days, particularly for patients with less severe disease. Â© 2009 Springer-Verlag.

Khemani R.G., Patel N.R., Bart R.D., Newth C.J.L. (2009). Comparison of the pulse oximetric saturation/fraction of inspired oxygen ratio and the Pao₂/fraction of inspired oxygen ratio in children, Chest, 135 (3), 662--668.

Background: Although diagnostic criteria for acute lung injury (ALI) and ARDS are clear, invasive arterial sampling is required for computation of Pao₂/fraction of inspired oxygen (FIO₂) [PF] ratios. The pulse oximetric saturation (Spo₂)/FIO₂ (SF) ratio may be a reliable noninvasive alternative to the PF ratio for identifying children with lung injury. Methods: We electronically queried blood gas measurements from two tertiary care pediatric ICUs (PICUs). Included in the analysis were corresponding measurements of Spo₂, Pao₂, and FIO ₂ charted within 15 min of each other when Spo₂ values were between 80% and 97%. Computed PF and SF ratios were compared to identify threshold values for SF ratios that correspond to PF criteria for ALI (â‰¤ 300) and ARDS (â‰¤ 200). Data from one PICU were used for derivation and validated with measurements from the second PICU. Results: From the 1,298 observations in the derivation data set, SF ratio could be predicted by the regression equation SF = 76 + 0.62 Ã— PF (p < 0.0001, R² = 0.61). SF ratios of 263 and 201 corresponded to PF ratios of 300 and 200, respectively. The ALI SF cutoff of 263 had 93% sensitivity and 43% specificity, and the ARDS cutoff of 201 had 84% sensitivity and 78% specificity. Applying these values to the 1,845 observations in the validation data set yielded a sensitivity of 86% and specificity of 47% for ALI and a sensitivity of 68% and specificity of 84% for ARDS. Conclusion: SF ratio is a reliable noninvasive marker for PF ratio to identify children with ALI or ARDS. Copyright Â© 2009 American College of Chest Physicians.

Pollack M.M., Holubkov R., Glass P., Dean J.M., Meert K.L., Zimmerman J., Anand K.J.S., Carcillo J., Newth C.J.L., Harrison R., Willson D.F., Nicholson C., Heidemann S., Frey M., Bell M., Reardon J., Prodhan P., Hefley G., Brogan T., Barker R., Venkataraman S.T., Abraham A., Fajardo J.F., Donaldson A., Burr J., Singh D., Enriquez R., Jenkins T., Cobb L.E., Gilles E., Sholas M., Matthews D. (2009). Functional status scale: New pediatric outcome measure, Pediatrics, 124 (1), --.

OBJECTIVE: The goal was to create a functional status outcome measure for large outcome studies that is well defined, quantitative, rapid, reliable, minimally dependent on subjective assessments, and applicable to hospitalized pediatric patients across a wide range of ages and inpatient environments. METHODS: Functional Status Scale (FSS) domains of functioning included mental status, sensory functioning, communication, motor functioning, feeding, and respiratory status, categorized from normal (score = 1) to very severe dysfunction (score = 5). The Adaptive Behavior Assessment System II (ABAS II) established construct validity and calibration within domains. Seven institutions provided PICU patients within 24 hours before or after PICU discharge, high-risk non-PICU patients within 24 hours after admission, and technology-dependent children. Primary care nurses completed the ABAS II. Statistical analyses were performed. RESULTS: A total of 836 children, with a mean FSS score of 10.3 (SD: 4.4), were studied. Eighteen percent had the minimal possible FSS score of 6, 44% had FSS scores of â‰¥10, 14% had FSS

scores of â‰¥15, and 6% had FSS scores of â‰¥20. Each FSS domain was associated with mean ABAS II scores (P < .0001). Cells in each domain were collapsed and reweighted, which improved correlations with ABAS II scores (P <.001 for improvements). Discrimination was very good for moderate and severe dysfunction (ABAS II categories) and improved with FSS weighting. Intraclass correlations of original and weighted total FSS scores were 0.95 and 0.94, respectively. CONCLUSIONS: The FSS met our objectives and is well suited for large outcome studies. Copyright Ã© 2009 by the American Academy of Pediatrics.

Zimmerman J.J., Akhtar S.R., Caldwell E., Rubenfeld G.D. (2009). Incidence and outcomes of pediatric acute lung injury, Pediatrics, 124 (1), 87--95.

OBJECTIVE: This population-based, prospective, cohort study was designed to determine the population incidence and outcomes of pediatric acute lung injury. METHODS: Between 1999 and 2000, 1 year of screening was performed at all hospitals admitting critically ill children in King County, Washington. County residents 0.5 to 15 years of age who required invasive (through endotracheal tube or tracheostomy) or noninvasive (through full face mask) mechanical ventilation, regardless of the duration of mechanical ventilation, were screened. From this population, children meeting North American-European Consensus Conference acute lung injury criteria were eligible for enrollment. Postoperative patients who received mechanical ventilation for <24 hours were excluded. Data collected included the presence of predefined cardiac conditions, demographic and physiological data, duration of mechanical ventilation, and deaths. US Census population figures were used to estimate incidence. Associations between outcomes and subgroups identified a priori were assessed. RESULTS: Thirty-nine children met the criteria for acute lung injury, resulting in a calculated incidence of 12.8 cases per 100 000 personyears. Severe sepsis (with pneumonia as the infection focus) was the most common risk factor. The median 24-hour Pediatric Risk of Mortality III score was 9.0, and the mean Â± SD was 11.7 Â± 7.5. The hospital mortality rate was 18%, lower than that reported previously for pediatric acute lung injury. There were no statistically significant associations between age, gender, or risk factors and outcomes. CONCLUSIONS: We present the first population-based estimate of pediatric acute lung injury incidence in the United States. Population incidence and mortality rates are lower than those for adult acute lung injury. Low mortality rates in pediatric acute lung injury may necessitate clinical trial outcome measures other than death. Copyright Â© 2009 by the American Academy of Pediatrics.

Anand K.J.S. (2008). Analgesia for skin-breaking procedures in newborns and children: What works best?, Canadian Medical Association Journal, 179 (1), 11--12.

[No abstract available]

Anand K.J.S., Anderson B.J., Holford N.H.G., Hall R.W., Young T., Shephard B., Desai N.S., Barton B.A. (2008). Morphine pharmacokinetics and pharmacodynamics in

preterm and term neonates: Secondary results from the NEOPAIN trial, British Journal of Anaesthesia, 101 (5), 680--689.

Background. Relationships between plasma morphine concentrations and neonatal responses to endotracheal tube (ETT) suctioning are unknown in preterm neonates. Methods. Ventilated preterm neonates (n=898) from 16 centres were randomly assigned to placebo (n=449) or morphine (n=449). After an i.v. loading dose (100 Î¼g kg-1), morphine infusions [23-26 weeks postmenstrual age (PMA) 10 Î¼g kg-1 h-1; 27-29 weeks 20 Î¼g kg -1 h-1; and 30-32 weeks 30 Î¼g kg-1 h -1] were established for a maximum of 14 days. Open-label morphine (20-100 Î¼g kg-1) was given for pain or agitation. Morphine assay and neonatal response to ETT suctioning was measured at 20-28 and 70-76 h after starting the drug infusion and at 10-14 h after discontinuation of the study drug. The concentration-effect response was investigated using non-linear mixed effects models. Results. A total of 5119 data points (1598 measured morphine concentrations and 3521 effect measures) were available from 875 neonates for analysis. Clearance was 50% that of the mature value at 54.2 weeks PMA (CLmat50) and increased from 2.05 litre h-1 70 kg -1 at 24 weeks PMA to 6.04 litre h-1 70 kg-1 at 32 weeks PMA. The volume of distribution in preterm neonates was 190 litre 70 kg-1 (CV 51%) and did not change with age. There was no relationship between morphine concentrations (range 0-440 Î¼g litre-1) and heart rate changes associated with ETT suctioning or with the Premature Infant Pain Profile. Conclusions. A sigmoid curve describing maturation of morphine clearance is moved to the right in preterm neonates and volume of distribution is increased compared with term neonates. Morphine does not alter the neonatal response to ETT suctioning. Â© The Board of Management and Trustees of the British Journal of Anaesthesia 2008. All rights reserved.

Anand K.J.S., Hall R.W. (2008). Love, pain, and intensive care, Pediatrics, 121 (4), 825--827.

[No abstract available]

Argent A.C., Hatherill M., Newth C.J.L., Klein M. (2008). The effect of epinephrine by nebulization on measures of airway obstruction in patients with acute severe croup, Intensive Care Medicine, 34 (1), 138--147.

Objectives: To demonstrate that tests of pulmonary function applicable to sick infants and small children with acute severe viral croup would provide clear, objective evidence of responsiveness to therapy with nebulized epinephrine. Study design: Oesophageal pressure changes and airflows at the mouth were measured in 17 patients with acute severe croup, before and after nebulization with epinephrine. Results: In 12 of the 17 patients there was a significant improvement in respiratory mechanics following epinephrine nebulization. Six of the 12 patients who responded to adrenaline also received 0.9% saline by nebulization, without improvement. No measures derived from combined flow and volume data showed any statistically significant change following epinephrine nebulization. Measures combining flow and pressure data, specifically inspiratory airway resistance, expiratory airway resistance, work of breathing, rate of work of breathing and volume for effort, showed changes of

26%, 33%, 16%, 16% and 46% respectively. The most statistically significant measures were pressure-rate product, pressure-time integral, oesophageal pressure alone and expiratory resistance. These changes persisted for at least 10 min after inhalation although there was some evidence of decline in pharmacologic effect at that time. Conclusions: Nebulized epinephrine results in a short-lived improvement in some but not all patients with croup. This reduction in respiratory effort occurs secondary to a decline in inspiratory and expiratory airway resistance. Oesophageal pressures measured via a feeding tube are satisfactory for quantification of the acute response and may be a useful continuous monitoring device. Flow measurements are unhelpful, and continuous administration of nebulized epinephrine should be investigated. Â© 2007 Springer-Verlag.

Argent A.C., Newth C.J.L., Klein M. (2008). The mechanics of breathing in children with acute severe croup, Intensive Care Medicine, 34 (2), 324--332.

Rationale: The assessment of the severity of croup and response to therapy has remained a clinical one. Despite recognition of the importance of a reproducible and easily applicable method for objectively measuring severity, currently, no such technique exists. Objectives: We postulated that measurements of air flow and intrathoracic pressure changes in patients with severe croup would provide detailed information about the mechanics of breathing and the potential for the development of continuous bedside methods for objective monitoring of upper airway obstruction. Methods: Twenty out of 21 eligible infants and children with severe upper airway obstruction from croup, and 5 control participants, were studied under light sedation utilizing face masks and nasogastric feeding tubes for flow and esophageal pressure measurements. Measurements and main results: Children with croup had lower tidal volumes, but breathed faster, thus maintaining similar minute volumes to the controls. During inspiration, all but 2 croup patients (but no controls) displayed flow limitation. Area within the flow-volume curve was significantly decreased and minute ventilation for effort expended was nearly 4.5 times higher in croup patients than in controls. Peak-to-trough pleural pressure swings, pressure-rate product and pressure-time integral were also significantly higher than in controls ($p < 0.001$) and returned to the normal range in the 9 patients who were subsequently intubated ($p < 0.001$). Conclusions: Patients with severe croup maintain minute ventilation by means of huge increases in intrathoracic pressure changes. Inspiratory flow limitation is present. In future outcome studies, measurements of respiratory function that do not include intrathoracic pressure changes are unlikely to be effective measures of the severity of croup. Â© 2007 Springer-Verlag.

Bell M.J., Kochanek P.M. (2008). Traumatic brain injury in children: Recent advances in management, Indian Journal of Pediatrics, 75 (11), 1159--1165.

To define and discuss new developments in the field of pediatric traumatic brain injury (TBI). Review of several recent key studies on therapy since publication of the first U.S. traumatic brain injury guidelines in 2003. In addition, we discuss new developments in the use of biomarkers of brain injury in TBI diagnosis and also discuss recent advances in bedside neuromonitoring that may be helpful in the setting of pediatric brain injury. Important new

information on optimal cerebral perfusion pressure management, cerebrospinal fluid drainage, decompressive craniectomy, hypothermia, biomarkers of brain injury along with advances in neuromonitoring are presented. The 2003 guidelines have stimulated important new research. This is reshaping bedside care. Â© 2008 Dr. K C Chaudhuri Foundation.

Hall R.W., Huitt T.W., Thapa R., Williams D.K., Anand K.J.S., Garcia-Rill E. (2008). Long-term deficits of preterm birth: Evidence for arousal and attentional disturbances, Clinical Neurophysiology, 119 (6), 1281--1291.

Objective: Quantitative measures of pre-attentional, attentional and frontal lobe processes were compared to evaluate quantitative measures of these deficits in Ex-Preterm vs. Ex-Term adolescents. Methods: We compared 43 Ex-Preterm with 26 Ex-Term adolescents using the P50 auditory potential, the Psychomotor Vigilance Task (PVT), a reaction time (RT) test, and Near Infrared Spectroscopy (NIRS). Results: The mean amplitude (Â±SE) of the P50 amplitude was similar in the Ex-Preterm (1.8 Â± 1.4 Î¼V) vs. Ex-Term adolescents (1.8 Â± 0.6 Î¼V, df = 68, F = 0.05, p = 0.8), but the Ex-Preterm group showed a trimodal distribution in amplitude (High, 3.3 Â± 0.4 Î¼V, df = 42.25, F = 19.2, p < 0.01; Medium, 1.7 Â± 0.1 Î¼V, df = 39, F = 0.41, p = 0.53; Low, 0.7 Â± 0.1 Î¼V, df = 40, F = 49.5, p < 0.01) suggested by statistically significant variance between populations (Kolmogorov-Kuiper test, df = 42.25, F = 5.4, p < 0.01). Mean RT was longer in Ex-Preterm (250 Â± 8 ms) vs. Ex-Term subjects (200 Â± 5 ms, df = 68, F = 18.8, p < 0.001). PVT lapses were increased in Ex-Preterm subjects, and varied inversely with P50 amplitude (Overall Mean 17 Â± 5 lapses, df = 67, F = 5.34, p < 0.05; Low P50 amplitude, 25 Â± 10, df = 40, F = 8.8, p < 0.01; Medium, 21 Â± 11, df = 38, F = 5.37, p < 0.05; High, 6 Â± 2, df = 39, F = 6.78, p < 0.01) vs. Ex-Term subjects (2 Â± 0.4 lapses, p < 0.01). NIRS levels did not differ statistically, but tended to correlate with P50 amplitude in the Ex-Preterm group. Conclusions: These findings suggest differential pre-attentional, attentional and frontal lobe dysfunction in Ex-Preterm adolescents. Significance: These measures could provide a means to objectively assess differential dysregulation of arousal and attention in Ex-Preterm adolescents, allowing optimization of therapeutic designs. Â© 2008 International Federation of Clinical Neurophysiology.

King M.A., Garrison M.M., Vavilala M.S., Zimmerman J.J., Rivara F.P. (2008). Complications associated with arterial catheterization in children, Pediatric Critical Care Medicine, 9 (4), 367--371.

To examine the prevalence of and risk factors associated with arterial catheterization complications in a large pediatric patient population in an effort to generate hypotheses for future prospective study of arterial catheter placement. Design: Retrospective cohort study. Setting: Patients discharged between January 1, 2000, and March 31, 2005, from 33 children's hospitals belonging to the Child Health Corporation of America. Patients: Patients were 10, 394 children identified from the Pediatric Health Information System database. Inclusion criteria included age 1 month to 18 yrs, admitted to a pediatric intensive care unit, received an arterial catheter for monitoring, and hospitalized for â‰¥1 day following catheter placement. Interventions: None.

Measurements and Main Results: We assessed complications as defined by ICD-9 coding associated with arterial catheterization, including thrombosis, embolism, and infection. Complications were reported in 10.3% (1, 072) of patients, most frequently infection/inflammation (61.8%), complication of vascular device not otherwise specified (14.9%), mechanical complications (14.1%), and embolic or thrombotic issues (7.5%). Independent predictors of complications associated with arterial catheterization were age (compared with 1-4 months) of 5-11 months (oddsratio [OR] 1.5; 95% confidence interval [CI] 1.25-1.82) or 1-2 yrs (OR 1.39; 95% CI 1.09 -1.78), insertion of catheters after the first hospital day and need for cardiac surgery (OR 1.31; 95% CI 1.03-1.68), bone marrow transplantation (OR 1.79; 95% CI 1.19- 2.70), and dialysis (OR 1.36; 95% CI 1.05-1.77). There was no association of arterial catheter complications with patient gender, Medicaid status, or presence of coagulopathy or shock. Conclusions: Complications associated with arterial catheterization are common in critically ill children. Significantly, we were unable to account for the potential confounding effect of central venous catheterization in this study secondary to limitations of ICD-9 coding. This study serves as a hypothesis-generating report of a large pediatric sample and suggests the need to carefully assess arterial catheter-associated complications in a prospective study independent of central venous catheters. (Pediatr Crit Care Med 2008; 9:367-371). Ã©2008 by the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies.

Meert K.L., Eggly S., Dean J.M., Pollack M., Zimmerman J., Anand K.J.S., Newth C.J.L., Willson D.F., Nicholson C. (2008). Ethical and logistical considerations of multicenter parental bereavement research, Journal of Palliative Medicine, 11 (3), 444--450.

Background: Multicenter research has the potential to recruit participants with diverse racial, ethnic, and geographic backgrounds and is essential for understanding heterogeneity in bereavement. The National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network (CPCCRN) is a multicenter network charged with conducting research on the pathophysiology and management of critical illness in childhood. Among its research activities, the CPCCRN has undertaken research in parental bereavement because most childhood deaths in the United States occur in hospitals, primarily in critical care units. Objective: The purpose of this paper is to discuss ethical and logistical issues found by the CPCCRN to be problematic to multicenter research with bereaved parents and to explore research strategies that may be practicably implemented. Results: Ethical and logistical challenges encountered by the CPCCRN included issues of privacy; confidentiality; voluntariness; minimizing risks; working with multiple institutional review boards; researcher qualifications, training and support; and methods of data collection. Strategies to address these challenges included local recruitment of participants; flexibility in consent methods across sites; participant options for methods of data collection; involvement of local bereavement support services; central training of researchers with systematic monitoring and opportunitieas for support; and use of a secure Web-based collaborative workspace. Conclusions: Multicenter parental bereavement research has distinct ethical issues that must be addressed by the logistics of

the research plan. Greater attention to the issues identified may facilitate research to reduce adverse mental and physical health outcomes in a diverse population of bereaved individuals. Â© 2008 Mary Ann Liebert, Inc.

Meert K.L., Eggly S., Pollack M., Anand K.J.S., Zimmerman J., Carcillo J., Newth C.J.L., Dean J.M., Willson D.F., Nicholson C., Heidemann S., Frey M., Albrecht T.L., Bell M., Reardon J., Romero S., Prodhan P., Hefley G., Brogan T., Barker R., Venkataraman S.T., Abraham A., Gold J.I., Ferguson E., Fajardo J.F., Harrison R., Burr J., Donaldson A., Holubkov R., Singh D., Enriquez R., Jenkins T. (2008). Parents' perspectives on physician-parent communication near the time of a child's death in the pediatric intensive care unit, Pediatric Critical Care Medicine, 9 (1), 2--7.

OBJECTIVE: Communicating bad news about a child's illness is a difficult task commonly faced by intensive care physicians. Greater understanding of parents' scope of experiences with bad news during their child's hospitalization will help physicians communicate more effectively. Our objective is to describe parents' perceptions of their conversations with physicians regarding their child's terminal illness and death in the pediatric intensive care unit (PICU). DESIGN: A secondary analysis of a qualitative interview study. SETTING: Six children's hospitals in the National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network. PARTICIPANTS: Fifty-six parents of 48 children who died in the PICU 3-12 months before the study. INTERVENTIONS: Parents participated in audio recorded semistructured telephone interviews. Interviews were analyzed using established qualitative methods. MEASUREMENTS AND MAIN RESULTS: Of the 56 parents interviewed, 40 (71%) wanted to provide feedback on the way information about their child's terminal illness and death was communicated by PICU physicians. The most common communication issue identified by parents was the physicians' availability and attentiveness to their informational needs. Other communication issues included honesty and comprehensiveness of information, affect with which information was provided, withholding of information, provision of false hope, complexity of vocabulary, pace of providing information, contradictory information, and physicians' body language. CONCLUSIONS: The way bad news is discussed by physicians is extremely important to most parents. Parents want physicians to be accessible and to provide honest and complete information with a caring affect, using lay language, and at a pace in accordance with their ability to comprehend. Withholding prognostic information from parents often leads to false hopes and feelings of anger, betrayal, and distrust. Future research is needed to investigate whether the way bad news is discussed influences psychological adjustment and family functioning among bereaved parents. Â©2008The Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies.

Menon G., Boyle E.M., Bergqvist L.L., McIntosh N., Barton B.A., Anand K.J.S. (2008). Morphine analgesia and gastrointestinal morbidity in preterm infants: Secondary results from the NEOPAIN trial, Archives of Disease in Childhood: Fetal and Neonatal Edition, 93 (5), --.

Objective: To investigate the influence of morphine therapy and other factors on the attainment of full enteral feeds and on acquired gastrointestinal pathology in preterm infants. Design: Secondary data analysis from a randomised, placebo controlled trial. Setting: 16 neonatal intensive care units in USA, Sweden, France and UK. Patients: 898 infants (treatment group 449, control 449). Gestation (median (range)): 27 (23-32) weeks; birth weight (median (range)): 985 (420-2440) g. Interventions: Morphine (M) or placebo (Pl) given preemptively by intravenous loading dose (100 Î¼g/kg of morphine) and infusion (10-30 Î¼g/kg/h depending on gestation) while infants were ventilated, for up to 14 days. "Open-label" morphine (A) could be given if clinically indicated. Main outcome measures: Age at full enteral feeds and major acquired gastrointestinal pathology. Results: The group randomised to morphine was later in attaining full feeds (median days (quartiles): M 20 (13-29), Pl 17 (12-26); p = 0.003), and in starting feeds (median days (quartiles): M 5 (3-8), Pl 4 (2-7)). In a linear regression model, age at full feeds was independently associated with birth weight, a score of neonatal morbidities, neonatal dexamethasone use and cumulative morphine dose. There was no relationship between morphine use and acquired gastrointestinal pathology (M 9/449, Pl 8/449; Ï‡2 p = 0.81). Conclusions: Morphine delays the attainment of full enteral feeds, partly by delaying the start of feeding, but does not discemibly increase gastrointestinal complications. The attainment of full feeds is influenced by morphine dose, but other factors seem to be important, including birth weight and neonatal morbidity.

Rovnaghi C.R., Garg S., Hall R.W., Bhutta A.T., Anand K.J.S. (2008). Ketamine analgesia for inflammatory pain in neonatal rats: A factorial randomized trial examining long-term effects, Behavioral and Brain Functions, 4 (), --.

Background: Neonatal rats exposed to repetitive inflammatory pain have altered behaviors in young adulthood, partly ameliorated by Ketamine analgesia. We examined the relationships between protein expression, neuronal survival and plasticity in the neonatal rat brain, and correlated these changes with adult cognitive behavior. Methods: Using Western immunoblot techniques, homogenates of cortical tissue were analyzed from neonatal rats 18-20 hours following repeated exposure to 4% formalin injections (F, N = 9), Ketamine (K, 2.5 mg/kg Ã— 2, N = 9), Ketamine prior to formalin (KF, N = 9), or undisturbed controls (C, N = 9). Brain tissues from another cohort of rat pups (F = 11, K = 12, KF = 10, C = 15) were used for cellular staining with Fos immunohistochemistry or FluoroJade-B (FJB), followed by cell counting in eleven cortical and three hippocampal areas. Long-term cognitive testing using a delayed non-match to sample (DNMS) paradigm in the 8-arm radial maze was performed in adult rats receiving the same treatments (F = 20, K = 24, KF = 21, C = 27) in the neonatal period. Results: Greater cell death occurred in F vs. C, K, KF in parietal and retrosplenial areas, vs. K, KF in piriform, temporal, and occipital areas, vs. C, K in frontal and hindlimb areas. In retrosplenial cortex, less Fos expression occurred in F vs. C, KF. Cell death correlated inversely with Fos expression in piriform, retrosplenial, and occipital areas, but only in F. Cortical expression of glial fibrillary acidic protein (GFAP) was elevated in F, K and KF vs. C. No significant differences occurred in Caspase-3, Bax, and Bcl-2 expression between groups, but cellular changes in cortical areas were

significantly correlated with protein expression patterns. Cluster analysis of the frequencies and durations of behaviors grouped them as exploratory, learning, preparatory, consumptive, and foraging behaviors. Neonatal inflammatory pain exposure reduced exploratory behaviors in adult males, learning and preparatory behaviors in females, whereas Ketamine ameliorated these long-term effects. Conclusion: Neuroprotective effects of Ketamine attenuate the impaired cognitive behaviors resulting from pain-induced cell death in the cortical and hippocampal fields of neonatal rats. This cell death was not dependent on the apoptosis associated proteins, but was correlated with glial activation. Â© 2008 Rovnaghi et al; licensee BioMed Central Ltd.

Anand K.J.S. (2007). Pain assessment in preterm neonates, Pediatrics, 119 (3), 605--607.

[No abstract available]

Anand K.J.S. (2007). Anesthetic neurotoxicity in newborns: Should we change clinical practice?, Anesthesiology, 107 (1), 2--4.

[No abstract available]

Anand K.J.S. (2007). Pharmacological approaches to the management of pain in the neonatal intensive care unit, Journal of Perinatology, 27 (), --.

Effective and consistent management of neonatal pain remains a controversial issue. Premature infants are repeatedly subjected to painful tests and procedures or suffer painful conditions when they are most vulnerable. With different mechanisms transducing various types of pain the practice of 'one-drug fits all' becomes questionable. Clinicians must use the latest non-pharmacologic and pharmacologic therapies for effective management of neonatal pain, distress, or agitation. Pharmacologic strategies for dealing with neonatal pain in the neonatal intensive care unit are described. Opioid therapy, once considered the mainstay for neonatal analgesia, may not be as effective as previously thought. Morphine infusions do not alter the neurological outcomes of preterm neonates and may not be effective against acute pain. Alternative approaches with methadone, ketamine, or local anesthetics should be considered. Clinicians must understand the contextual circumstances underlying pain in individual neonates and tailor therapy accordingly, using the most current evidence related to neonatal pain assessment and management.

Anand K.J.S. (2007). Consciousness, cortical function, and pain perception in nonverbal humans, Behavioral and Brain Sciences, 30 (1), 82--83.

Postulating the subcortical organization of human consciousness provides a critical link for the construal of pain in patients with impaired cortical function or cortical immaturity during early development. Practical implications of the centrencephalic proposal include the redefinition of pain, improved pain assessment in nonverbal humans, and benefits of adequate analgesia/anesthesia for these patients, which certainly justify the rigorous scientific efforts required. Â© 2007 Cambridge University Press.

Anand K.J.S., Garg S., Rovnaghi C.R., Narsinghani U., Bhutta A.T., Hall R.W. (2007). Ketamine reduces the cell death following inflammatory pain in newborn rat brain, Pediatric Research, 62 (3), 283--290.

Premature infants experience untreated repetitive pain that may alter their brain development. Effects of ketamine and repetitive pain on cellular death and subsequent behavior were studied in neonatal rats. Rat pups were randomized to undisturbed controls (C), 4% formalin injection (F), ketamine alone (K, 5 mg/kg) or formalin plus ketamine (KF) and were assessed for neuroactivation with Fos protein, cellular death with FluoroJade-B, cognition with the radial arm maze, and pain thresholds with the hot-plate. Greater Fos expression and cell death occurred in F vs. C groups in defined brain areas at 1 and 4 h in F compared with other groups. Cell death was accentuated 3.3-fold in cortical areas and 1.6-fold in subcortical areas in the F compared with the C group following repetitive pain and sacrifice 18-20 h later. These effects were ameliorated by ketamine. Compared with the F group, all other groups demonstrated greater exploratory and rearing behaviors and decreased time for bait consumption at 1-h and 3-h intervals. Significantly greater thermal pain latencies occurred in the KF and F groups. Repetitive neonatal pain accentuates neuronal excitation and cell death in developmentally regulated cortical and subcortical areas, which decreases the acquisition of visual-spatial clues, short-term and long-term memory, and increases pain latencies. Ketamine analgesia mitigates most of these effects.

Anand K.J.S., Hall R.W. (2007). Controversies in Neonatal Pain: An Introduction, Seminars in Perinatology, 31 (5), 273--274.

[No abstract available]

Anand K.J.S., Westrup B., Seri I. (2007). Discussion 1: Management of pain in the neonate, Journal of Perinatology, 27 (), --.

[No abstract available]

Bergqvist L.L., Eriksson M., Kronsberg S.S., Schollin J., Barton B., Anand K.J.S. (2007). Seeing through the blind! Ability of hospital staff to differentiate morphine from placebo, in neonates at a placebo controlled trial, Acta Paediatrica, International Journal of Paediatrics, 96 (7), 1004--1007.

Aim: To investigate whether professional training and/or clinical experience affect the ability of caregiver to assess clinical signs of pre-emptive morphine analgesia. Methods: In the Neurological Outcomes & Pre-emptive Analgesia In Neonates trial preterm infants undergoing mechanical ventilation were randomized to receive continuous infusion, either of morphine or placebo blinded. Staff from centres in Sweden (Stockholm and Ã–rebro) completed an assessment form. Results: A total of 360 assessment forms were collected from 52 neonates. In 59% of the cases, caregivers correctly identified patients group. Comparable proportion of answers were correct between physicians, nurses and

assistant nurses (63, 60 and 54%, respectively, p = 0.60). Staff with Neonatal intensive care unit experience <1 year identified 63%, as compared to 65% for working 1-5 year, and 55% that has been working >5 years (p = 0.28). Staff's ability to correctly identify group assignment was reduced by amount of additional morphine (p < 0.01) and severity of illness (p = 0.01). Conclusions: Clinical medical staffs, including neonatologists, have great difficulties in assessing the presence and severity of pain. Further studies should focus on the methods for assessment of prolonged pain in preterm neonates, define the effects of adequate analgesia, and investigate the clinical factors that may alter neonatal responses to acute and prolonged pain. Ã© 2007 The Author(s).

Bhutta A., Gilliam C., Honeycutt M., Schexnayder S., Green J., Moss M., Anand K.J.S. (2007). Reduction of bloodstream infections associated with catheters in paediatric intensive care unit: Stepwise approach, British Medical Journal, 334 (7589), 362--365.

Problem: Bloodstream infections associated with catheters were the most common nosocomial infections in one paediatric intensive care unit in 1994-7, with rates well above the national average. Design: Clinical data were collected prospectively to assess the rates of infection from 1994 onwards. The high rates in 1994-7 led to the stepwise introduction of interventions over a five year period. At quarterly intervals, prospective data continued to be collected during this period and an additional three year follow-up period. Setting: A 292 bed tertiary care children's hospital. Key measures fer improvement: We aimed to reduce our infection rates to below the national mean rates for similar units by 2000 (a 25% reduction). Strategies for change A stepwise introduction of interventions designed to reduce infection rates, including maximal barrier precautions, transition to antibiotic impregnated central venous catheters, annual handwashing campaigns, and changing the skin disinfectant from povidone-iodine to chlorhexidine. Effects of change: Significant decreases in rates of infection occurred over the intervention period. These were sustained over the three year follow-up. Annual rates decreased from 9.7/1000 days with a central venous catheter in 1997 to 3.0/1000 days in 2005, which translates to a relative risk reduction of 75% (95% confidence interval 35% to 126%), an absolute risk reduction of 6% (2% to 10%), and a number needed to treat of 16 (10 to 35). Lessons learnt: A stepwise introduction of interventions leading to a greater than threefold reduction in nosocomial infections can be implemented successfully. This requires a multidisciplinary team, support from hospital leadership, ongoing data collection, shared data interpretation, and introduction of evidence based interventions.

Bhutta A.T., Venkatesan A.K., Rovnaghi C.R., Anand K.J.S. (2007). Anaesthetic neurotoxicity in rodents: Is the ketamine controversy real?, Acta Paediatrica, International Journal of Paediatrics, 96 (11), 1554--1556.

[No abstract available]

Boyle E.M., Freer Y., Wong C.M., McIntosh N., Anand K.J.S. (2007). Response to PAIN Editorial re: Boyle et al. (2006), Pain, 127 (3), 302--.

[No abstract available]

Carbajal R., Eble B., Anand K.J.S. (2007). Premedication for Tracheal Intubation in Neonates: Confusion or Controversy?, Seminars in Perinatology, 31 (5), 309--317.

Tracheal intubation is performed frequently in the NICU and delivery room. This procedure is extremely distressing, painful, and has the potential for airway injury. Premedication with sedatives, analgesics, and muscle relaxants is standard practice for pediatric and adult intubation, yet the use of these drugs is not common for intubation in neonates. The risks and benefits of using premedications for intubating unstable newborns are hotly debated, although recent evidence shows that premedication for non-urgent or semi-urgent intubations is safer and more effective than awake intubations. This article reviews clinical practices reported in surveys on premedication for neonatal intubation, the physiological effects of laryngoscopy and intubation on awake neonates, as well as the clinical and physiological effects of different drug combinations used for intubation. A wide variety of drugs, either alone or in combination, have been used as premedication for elective intubation in neonates. Schematically, these studies have been of three main types: (a) studies comparing awake intubation versus those with sedation or analgesia, (b) studies comparing different premedication regimens comprising sedatives, analgesics, and anesthetics, and (c) case series of neonates in which some authors have reported their experience with a specific premedication regimen. The clinical benefits described in these studies and the need for pain control in neonates make the case for using appropriate premedication routinely for elective or semi-urgent intubations. Tracheal intubation without the use of analgesia or sedation should be performed only for urgent resuscitations in the delivery room or other life-threatening situations when intravenous access is unavailable. Â© 2007 Elsevier Inc. All rights reserved.

Cheung C.L.S., Van Dijk M., Green J.W., Tibboel D., Anand K.J.S. (2007). Effects of low-dose naloxone on opioid therapy in pediatric patients: A retrospective case-control study, Intensive Care Medicine, 33 (1), 190--194.

Objective: To develop novel therapies that prevent opioid tolerance in critically ill children we examined the effects of low-dose naloxone infusions on patients' needs for analgesia or sedation. Design and setting: Matched case-control study in a pediatric intensive care unit at a university children's hospital. Patients: We compared 14 pediatric ICU patients receiving low-dose naloxone and opioid infusions with 12 matched controls receiving opioid infusions. Measurements and main results: Opioid analgesia and sedative requirements were assessed as morphine- and midazolam-equivalent doses, respectively. No differences were observed between groups in opioid doses at baseline or during naloxone, but in the postnaloxone period opioid doses tended to be lower in the naloxone group. Compared to baseline the naloxone group required more opioids during naloxone but fewer opioids after naloxone. Total sedative doses were comparable at baseline in both groups, with no differences in the postnaloxone period. The naloxone group required less sedation after naloxone but sedation doses were unchanged in controls. The two groups did not differ in pain scores, sedation scores, or opioid side effects. Conclusions: Naloxone did not reduce the need for opioid during the infusion period but tended to reduce opioid

requirements in the postnaloxone period without additional need for sedation. Randomized clinical trials may examine the effects of low-dose naloxone on opioid tolerance and side effects in pediatric ICU patients requiring prolonged opioid analgesia. Â© 2006 Springer-Verlag.

Clancy B., Kersh B., Hyde J., Darlington R.B., Anand K.J.S., Finlay B.L. (2007). Web-based method for translating neurodevelopment from laboratory species to humans, Neuroinformatics, 5 (1), 79--94.

Biomedical researchers and medical professionals are regularly required to compare a vast quantity of neurodevelopmental literature obtained from an assortment of mammals whose brains grow at diverse rates, including fast developing experimental rodent species and slower developing humans. In this article, we introduce a database-driven website, which was created to address this problem using statistical-based algorithms to integrate hundreds of empirically derived developing neural events in 10 mammalian species (http://translatingtime.net/). The site, based on a statistical model that has evolved over the past decade, currently incorporates 102 different neurodevelopmental events obtained from 10 species: hamsters, mice, rats, rabbits, spiny mice, guinea pigs, ferrets, cats, rhesus monkeys, and humans. Data are arranged in a Structured Query Language database, which allows comparative brain development measured in postconception days to be converted and accessed in real time, using Hypertext Preprocessor language. Algorithms applied to the database also allow predictions for dates of specific neurodevelopmental events where empirical data are not available, including for the human embryo and fetus. By designing a web-based portal, we seek to make these comparative data readily available to all those who need to efficiently estimate the timing of neurodevelopmental events in the human fetus, laboratory species, or across several different species. In an effort to further refine and expand the applicability of this database, we include a mechanism to submit additional data.

Golianu B., Krane E., Seybold J., Almgren C., Anand K.J.S. (2007). Non-Pharmacological Techniques for Pain Management in Neonates, Seminars in Perinatology, 31 (5), 318--322.

Significant progress in understanding the physiology, clinical correlates, and consequences of neonatal pain have resulted in greater attention to pain management during neonatal intensive care. A number of nonpharmacological therapies have been investigated, including nonnutritive sucking, with and without sucrose use, swaddling or facilitated tucking, kangaroo care, music therapy, and multi-sensorial stimulation. Although the efficacy of these approaches is clearly evident, they cannot provide analgesia for moderate or severe pain in the neonate. Further, some of these therapies cannot be effectively applied to all populations of critically ill neonates. Acupuncture, an ancient practice in Chinese medicine, has gained increasing popularity for symptom control among adults and older children. Acupuncture may provide an effective nonpharmacological approach for the treatment of pain in neonates, even moderate or severe pain, and should be considered for inclusion in a

graduated multidisciplinary algorithm for neonatal pain management. Â© 2007 Elsevier Inc. All rights reserved.

Graham A.S., Chandrashekharaiah G., Citak A., Wetzel R.C., Newth C.J.L. (2007). Positive end-expiratory pressure and pressure support in peripheral airways obstruction: Work of breathing in intubated children, Intensive Care Medicine, 33 (1), 120--127.

Objectives: Children with peripheral airways obstruction suffer the negative effects of intrinsic positive end-expiratory pressure: increased work of breathing and difficulty triggering assisted ventilatory support. We examined whether external positive end-expiratory pressure to offset intrinsic positive end-expiratory pressure decreases work of breathing in children with peripheral airways obstruction. The change in work of breathing with incremental pressure support was also tested. Design and setting: Prospective clinical trial in a pediatric intensive care unit. Patients: Eleven mechanically ventilated, spontaneously breathing children with peripheral airways obstruction. Interventions: Work of breathing (using pressure-rate product as a surrogate) was measured in three tiers: (a) Increasing pressure support over zero end-expiratory pressure. (b) Increasing applied positive end-expiratory pressure and fixed pressure support. The level of applied positive end-expiratory pressure at which pressure-rate product was least determined the compensatory positive end-expiratory pressure. (c) Increasing pressure support over compensatory (fixed) positive end-expiratory pressure. Measurements and results: Increases in pressure support alone decreased pressure-rate product from mean 724 Â± 311 to 403 Â± 192 cmH2O/min. Applied positive end-expiratory pressure alone decreased pressure-rate product from mean 608 Â± 301 to 250 Â± 169 cmH2O/min. The lowest pressure-rate product (136 Â± 128 cmH2O/min) was achieved using compensatory positive end-expiratory pressure (12 Â± 4 cmH2O) with pressure support 16 cmH2O. Conclusions: For children with peripheral airways obstruction who require assisted ventilation, work of breathing during spontaneous breaths is decreased by the application of either compensatory positive end-expiratory pressure or pressure support. Â© 2006 Springer-Verlag.

Lowery C.L., Hardman M.P., Manning N., Hall R.W., Anand K.J.S. (2007). Neurodevelopmental Changes of Fetal Pain, Seminars in Perinatology, 31 (5), 275--282.

Pain in the developing fetus is controversial because of the difficulty in measuring and interpreting pain during gestation. It has received increased attention lately because of recently introduced legislation that would require consideration of fetal pain during intentional termination of pregnancy. During development, sensory fibers are abundant by 20 weeks; a functional spinal reflex is present by 19 weeks; connections to the thalamus are present by 20 weeks; and connections to subplate neurons are present by 17 weeks with intensive differentiation by 25 weeks. These cells are important developmentally, but decline as a result of natural apoptosis. Mature thalamocortical projections are not present until 29 to 30 weeks, which has led many to believe the fetus does not experience emotional "pain" until then. Pain requires both nociception and emotional reaction or interpretation. Nociception

causes physiologic stress, which in turn causes increases in catecholamines, cortisol, and other stress hormones. Physiological stress is different from the emotional pain felt by the more mature fetus or infant, and this stress is mitigated by pain medication such as opiates. The plasticity of the developing brain makes it vulnerable to the stressors that cause long-term developmental changes, ultimately leading to adverse neurological outcomes. Whereas evidence for conscious pain perception is indirect, evidence for the subconscious incorporation of pain into neurological development and plasticity is incontrovertible. Scientific data, not religious or political conviction, should guide the desperately needed research in this field. In the meantime, it seems prudent to avoid pain during gestation.

Meert K.L., Eggly S., Pollack M., Anand K.J.S., Zimmerman J., Carcillo J., Newth C.J.L., Dean J.M., Willson D.F., Nicholson C. (2007). Parents' Perspectives Regarding a Physician-Parent Conference after Their Child's Death in the Pediatric Intensive Care Unit, Journal of Pediatrics, 151 (1), --.

Objective: To investigate parents' perspectives on the desirability, content, and conditions of a physician-parent conference after their child's death in the pediatric intensive care unit (PICU). Study design: Audio-recorded telephone interviews were conducted with 56 parents of 48 children. All children died in the PICU of one of six children's hospitals in the National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network (CPCCRN) 3 to 12 months before the study. Results: Only seven (13%) parents had a scheduled meeting with any physician to discuss their child's death; 33 (59%) wanted to meet with their child's intensive care physician. Of these, 27 (82%) were willing to return to the hospital to meet. Topics that parents wanted to discuss included the chronology of events leading to PICU admission and death, cause of death, treatment, autopsy, genetic risk, medical documents, withdrawal of life support, ways to help others, bereavement support, and what to tell family. Parents sought reassurance and the opportunity to voice complaints and express gratitude. Conclusions: Many bereaved parents want to meet with the intensive care physician after their child's death. Parents seek to gain information and emotional support, and to give feedback about their PICU experience.

Okhuysen-Cawley R., Prodhan P., Imamura M., Dedman A.H., Anand K.J.S. (2007). Management of abdominal compartment syndrome during extracorporeal life support, Pediatric Critical Care Medicine, 8 (2), 177--179.

OBJECTIVE: To describe the successful use of a peritoneal dialysis catheter for emergent decompression of abdominal compartment syndrome during extracorporeal life support for septic shock. DESIGN: Case report. SETTING: Pediatric intensive care unit at a freestanding tertiary children's hospital. PATIENT: Two-year-old toddler with influenza A complicated by methicillin-resistant Staphylococcus aureus pneumonia and septic shock. INTERVENTIONS: Placement of peritoneal dialysis catheter. MEASUREMENTS AND MAIN RESULTS: Changes in hemodynamic and respiratory parameters.

Improvement in extracorporeal membrane oxygenation venous drainage with subsequent survival. CONCLUSIONS: Although the standard therapy for abdominal compartment syndrome is decompressive laparotomy, a minimally invasive percutaneous approach may be effective and should be considered in selected patients. Â©2007The Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies.

Ranger M., Johnston C.C., Anand K.J.S. (2007). Current Controversies Regarding Pain Assessment in Neonates, Seminars in Perinatology, 31 (5), 283--288.

Although over 40 methods of pain assessment in infants are available for use in clinical practice, unrecognized and under-treated pain remains one of the most commonly reported problems within the Neonatal Intensive Care Units. A number of factors have been found to account for differences in the robustness of the pain response in neonates of varying gestational ages. Discrepancies between behavioral and physiological pain indicators have also been reported. With newer technologies, there is an opportunity not only to verify infant pain perception, but these tools may allow an identification of which of the observed indicators are most sensitive in particular clinical situations. The current controversies regarding pain assessment in preterm and term infants are reviewed to define the most important issues and to develop a dialogue for future directions. Â© 2007 Elsevier Inc. All rights reserved.

Smith A.B., Hefley G.C., Anand K.J. (2007). Parent bed spaces in the PICU: effect on parental stress., Pediatric nursing, 33 (3), 215--221.

The purpose of this comparative descriptive study was to identify the impact of providing a parent bed space in the PICU, allowing for continual parental presence, on stress of the parents of critically ill children. Data were collected from parents (n = 86) at two children's hospitals 3 months prior to the opening of new PICUs with parent bed spaces. Following a transition period, data were collected from a sample of parents (n = 92) who had used the parent bed to stay overnight with their child. Parental stress was measured with the Parental Stressor Scale: Pediatric Intensive Care (PSS: PICU). Stress scores were significantly lower (p = .02) for parents who utilized the parent beds in the new PICUs. New PICU environments that facilitate continual parental presence may reduce parental stress related to a child's hospitalization.

Underwood K., Rubin S., Deakers T., Newth C. (2007). Infant botulism: A 30-year experience spanning the introduction of botulism immune globulin intravenous in the intensive care unit at Childrens Hospital Los Angeles, Pediatrics, 120 (6), --.

OBJECTIVE. To report a tertiary care hospital's 30-year experience with the diagnosis, treatment, and outcome of infant botulism in the PICU before and after the availability of Botulism Immune Globulin Intravenous. METHODS. This was a retrospective medical chart review of the 67 patients who had received a diagnosis of infant botulism and were admitted to the ICU from 1976 to 2005. The ages on presentation, length of hospital stay, length of ICU stay, length of mechanical ventilation, and type of botulism toxin were recorded and compared for patients who had received Botulism Immune Globulin

Intravenous and those who had not. On the basis of our results, conclusions were drawn regarding the effect of Botulism Immune Globulin Intravenous on the morbidity of infant botulism. RESULTS. Sixty-seven patients' charts were reviewed; 23 male and 29 female patients did not receive Botulism Immune Globulin Intravenous. Of patients who did not receive Botulism Immune Globulin Intravenous, the median age at presentation was 71 days, median length of hospital stay was 35 days, ICU stay was 24 days, and duration of mechanical ventilation was 17 days. A total of 40% had type A toxin, and 60% had type B toxin. There was a significant difference between patients with toxin types A and B in length of hospital stay but not length of ICU stay or mechanical ventilation. Patients with type A toxin were significantly older than patients with type B toxin. Fifteen children received Botulism Immune Globulin Intravenous. There were statistically significant differences in length of hospital stay, length of ICU stay, and length of mechanical ventilation between patients who received Botulism Immune Globulin Intravenous and those who did not. CONCLUSIONS. The use of Botulism Immune Globulin Intravenous significantly decreased the length of ICU stay, length of mechanical ventilation, and overall hospital stay in children with infant botulism. Copyright Â© 2007 by the American Academy of Pediatrics.

Zimmerman J.J. (2007). A history of adjunctive glucocorticoid treatment for pediatric sepsis: Moving beyond steroid pulp fiction toward evidence-based medicine, Pediatric Critical Care Medicine, 8 (6), 530--539.

OBJECTIVES: To review the history of clinical use of corticosteroids with particular reference to adjunctive therapy for severe pediatric sepsis and, in this context, to provide an overview of what is known, what is not known, and what research questions are particularly relevant at this time. DATA SOURCE: Literature review using PubMed, cross-referenced article citations, and the Internet. CONCLUSIONS: The history of corticosteroid use in clinical medicine has been colorful, noisy, and always controversial. Therapeutic corticosteroid indications that initially seemed rational have frequently been refuted on closer, rigorous clinical trial inspection. Although it may be prudent to provide stress-dose steroids to children with septic shock who are clinically at risk for adrenal insufficiency (chronic or recent steroid use, purpura fulminans, etomidate or ketoconazole administration, hypothalamic, pituitary, adrenal disease), the safety and efficacy of stress-dose steroids as general adjunctive therapy for pediatric septic shock have not been established. Glucocorticoid administration does add potential risk to critically ill children. In particular, although adjunctive corticosteroids may hasten resolution of unstable hemodynamics in septic shock, this may occur at the metabolic cost of hyperglycemia. Clinical practice that fosters innovative therapy (off-label use) over research probably represents bad medical and social policy. Accordingly, pediatric critical care researchers have a responsibility to generate pediatric-specific evidence-based medicine for adjunctive corticosteroid therapy for severe sepsis in children. Ã© 2007 The Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies.

Zimmerman J.J. (2007). Testing the waters, Pediatric Critical Care Medicine, 8 (3), 305--307.

[No abstract available]

Zimmerman J.J. (2007). Moving beyond Babel, Pediatric Critical Care Medicine, 8 (1), 73--75.

[No abstract available]

Anand K.J.S., Hall R.W. (2006). Pharmacological therapy for analgesia and sedation in the newborn, Archives of Disease in Childhood: Fetal and Neonatal Edition, 91 (6), --.

Rapid advances have been made in the use of pharmacological analgesia and sedation for newborns requiring neonatal intensive care. Practical considerations for the use of systemic analgesics (opioids, non-steroidal anti-inflammatory agents, other drugs), local and topical anaesthetics, and sedative or anaesthetic agents (benzodiazepines, barbiturates, other drugs) are summarised using an evidence-based medicine approach, while avoiding mention of the underlying basic physiology or pharmacology. These developments have inspired more humane approaches to neonatal intensive care. Despite these advances, little is known about the clinical effectiveness, immediate toxicity, effects on special patient populations, or long-term effects after neonatal exposure to analgesics or sedatives. The desired or adverse effects of drug combinations, interactions with non-pharmacological interventions or use for specific conditions also remain unknown. Despite the huge gaps in our knowledge, preliminary evidence for the use of neonatal analgesia and sedation is available, but must be combined with a clear definition of clinical goals, continuous physiological monitoring, evaluation of side effects or tolerance, and consideration of long-term clinical outcomes.

Taylor B.J., Robbins J.M., Gold J.I., Logsdon T.R., Bird T.M., Anand K.J.S. (2006). Assessing postoperative pain in neonates: A multicenter observational study, Pediatrics, 118 (4), --.

OBJECTIVE. A multicenter observational study was conducted to evaluate the practices of postoperative pain assessment and management in neonates to identify specific targets for improvement in clinical practice. METHODS. Ten participating NICUs collected data for the 72 hours after a surgical operation on 25 consecutive neonates (N = 250), including demographics, principal diagnoses, operative procedure, other painful procedures, pain assessments, interventions (pharmacologic and nonpharmacologic), and adverse events in neonates who underwent minor and major surgery. Descriptive and logistic-regression analyses were performed by using SPSS and Stata. RESULTS. The neonates studied had a birth weight of 2.4 Â± 1.0 kg (mean Â± SD) and gestational age of 36 Â± 4.3 weeks; 57% were male, and length of hospital stay was 23.5 Â± 30.0 days. Participating hospitals used 7 different numeric pain scales, with nursing pain assessments documented for 88% (n = 220) of the patients and physician pain assessments documented for 9% (n = 23) of the patients. Opioids (84% vs 60%) and benzodiazepines (24% vs 11%) were used

more commonly after major surgery than minor surgery, and a small proportion (7% major surgery, 12% minor surgery) received no analgesia. Logistic-regression analyses showed that physician pain assessment was the only significant predictor of postsurgical analgesic use, whereas major surgery and postnatal age in days did not seem to contribute. Physician pain assessment was documented for 23 patients; 22 of these received postoperative analgesia. CONCLUSIONS. Documentation of postoperative pain assessment and management in neonates was extremely variable among the participating hospitals. Pain assessment by physicians must be emphasized, in addition to developing evidence-based guidelines for postoperative care and educating professional staff to improve postoperative pain control in neonates. Copyright Ã© 2006 by the American Academy of Pediatrics.

Willson D.F., Dean J.M., Newth C., Pollack M., Anand K.J.S., Meert K., Carcillo J., Zimmerman J., Nicholson C. (2006). Collaborative Pediatric Critical Care Research Network (CPCCRN), Pediatric Critical Care Medicine, 7 (4), 301--307.

Pediatric critical care was formally recognized as a separate subspecialty in pediatrics in 1987. Since that time the numbers of pediatric intensivists, pediatric intensive care units, and pediatric intensive care beds in the United States have increased dramatically. Research efforts have lagged behind, however, as this new discipline has struggled to identify the necessary time, funding, and other resources to pursue clinical and laboratory investigation. In April 2004, the National Center for Medical Rehabilitation Research of the National Institute for Child Health and Human Development issued a request for applications to establish the Collaborative Pediatric Critical Care Research Network (CPCCRN). The CPCCRN provides an infrastructure to pursue collaborative clinical trials and descriptive studies in pediatric critical care medicine. Six pediatric centers involving seven intensive care units and a data-coordinating center were identified through a competitive application process. Network goals include the support of collaborative clinical trials otherwise impracticable in single institutions and the establishment of a framework for developing the scientific basis for pediatric critical care practice. This article describes how the CPCCRN was established, its organization, and its goals and future plans. Copyright Â© 2006 by the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies.