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The Collaborative Pediatric Critical Care Research Network: Looking back and Moving Forward

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Abstract

Objective—To update the Pediatric Critical Care Community on the progress of the Collaborative Pediatric Critical Care Research Network (CPCCRN) and plans for the future.

Setting—The six sites, seven hospitals of the CPCCRN.

Results—Since its inception in August 2005 the Network has engaged in a number of observational and interventional trials, several of which are ongoing. Several additional studies are in the planning stages. To date these have resulted in the publication of 6 manuscripts and 5 abstracts, with 5 additional manuscripts accepted and *in press*.

Conclusion—The Network remains committed to its stated goal "to initiate a multi-centered 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".

Keywords

Collaborative Pediatric Critical Care Research Network; NICHD; bereavement; corticosteroids; sepsis; severity scoring systems; metoclopramide; zinc; selenium; glutamine; pertussis; opioid tolerance; withdrawal; pulmonary hypertension; decision support; weaning; cardiac arrest; hypothermia; asthma

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Introduction

In April, 2004 the National Institute for Child Health and Human Development (now named for Eunice Kennedy Shriver) issued a Request for Applications (RFA) to establish a pediatric critical care research network "to initiate a multi-centered 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" (1). In January 2005 six sites (7 hospitals) and a data-coordinating center (DCC) were selected. The clinical sites and DCC Principal Investigators (PIs) are listed in the authorship of this paper. In the first four years, the CPCCRN has engaged in a number of observational studies and one interventional trial. Several have been completed, others are ongoing, and many are in various stages of planning and development. The purpose of this report is to update the pediatric critical care community about CPCCRN activities to date.

Current Studies in the CPCCRN

The CPCCRN Core Data Project (Registry)

The registry is a core data set from all patients admitted to Network pediatric intensive care units (PICUs) beginning in calendar year 2004. Compiled under the direction of J. Michael Dean and the DCC, the registry defines the patient population available for any future Network studies as well as offering insight into the composition of and outcomes in our pediatric critical care patient population (2). Approximately 10,000 patient admissions are added yearly.

Bereavement Studies

Grieving is a normal response to the loss of a child. How pediatric intensive care physicians might better support parents in healthy grieving is the subject of a series of studies designed by Kathleen Meert and undertaken by the CPCCRN. The ultimate goal is to develop and test a postmortem conference for bereaved families focused on the prevention of complicated grief. The first phase of the study, now completed, interviewed bereaved parents to determine what they felt would be the appropriate content and who should participate in a bereavement conference (3–9). One finding of the study is that postmortem conferences were desired by 60% of bereaved parents but actually occurred in only 13% (3). The second phase of this project, currently in progress, utilizes a variety of self-report instruments, among them the Inventory of Complicated Grief, to assess the incidence of complicated grief. Additionally, a study to examine physicians' attitudes about a physician-parent postmortem conference is ongoing (10). Knowledge gained from these studies will be used to design an effective postmortem conferences and measure their effect in assisting grieving parents.

Critical Illness Stress-Induced Immune Suppression Prevention Trial (CRISIS)

The Network's interventional study is the CRISIS prevention trial (11), designed by Joseph Carcillo. The study is a blinded, randomized controlled trial (RCT) of the efficacy of enteral supplementation with zinc, selenium, glutamine, and twice daily intravenous metoclopramide compared to standard therapy to reduce rates of nosocomial infection and sepsis in critically ill children. Each of the study agents has independently been demonstrated to prevent or ameliorate stress-induced lymphopenia (12–22). Lymphopenia (an absolute lymphocyte count < 1,200/mm^3) has been shown to precede sepsis and be associated with higher mortality (23). The combination therapy is hypothesized to constitute a form of "immune prophylaxis" to maintain lymphocyte health, akin to the use of heparin to prevent deep venous thrombosis (DVTs) or H_2 blockers to prevent stress-induced

gastritis. To date the study has enrolled approximately 250 subjects, with a study target enrollment of 600.

Functional Outcome Assessment in the Pediatric ICU (PICU)

Current severity scoring systems in pediatric critical care dichotomize outcomes to survival versus death (24,25). As mortality rates in pediatric critical care have decreased the need for predictors of the quality of survival has become apparent. The "Functional Status Score" (FSS) by Murray Pollack was designed to create an outcome measure that is well defined, quantitative, rapid, reliable, minimally dependent on subjective assessments, and applicable across the childhood age range (from full term newborns to adolescents). The scoring system, conceptually based on the adult concept of "activities of daily living", consists of 6 domains (mental status, sensory, communication, motor, feeding, and respiratory) categorized from normal (1) to severe dysfunction (5) that can be easily observed and reliably scored at any time during the hospitalization, including ICU and hospital discharge. The FSS was tested in 836 Network children at PICU and hospital discharge and demonstrated excellent discrimination, inter-rater reliability, and high correlation with the more complex adaptive behavior scales (26, 27).

Critical Pertussis in U.S. Children: Morbidity, Mortality, and Sequelae

Despite high immunization coverage rates in the USA, pertussis is still seen in most PICUs; usually, but not always in young infants (28). Deaths still occur, although most infants survive (29), and the incidence of longer term neurological, developmental, and respiratory sequelae in survivors remains unstudied (30–32). The critical pertussis study is a prospective cohort study to examine the acute course of pertussis in critically ill infants, assess developmental status and quality of life among survivors, and identify risk factors associated with suboptimal outcomes and sequelae. The study is a trans-Federal effort enabled by additional Department of Health and Human Services (DHHS) funding provided through the National Vaccine Program Office (NVPO) and involving collaboration with the Centers for Disease Control and Prevention, and a basic scientist supported by the National Institute of General Medical Sciences (NIGMS). NICHD CPCCRN Project Scientist (Carol Nicholson) serves as PI and all sites in the CPCCRN and approximately 20 outside sites, many from the Pediatric Acute Lung Injury and Sepsis Investigators Network (PALISI), are currently enrolling subjects.

Studies of Pediatric Septic Shock

Severe sepsis accounts for approximately 7% of all deaths in children (33,34). Because many believe sepsis is accompanied by relative adrenal insufficiency, corticosteroids are frequently administered despite lack of evidence of improved long-term outcomes (35,36). Jerry Zimmerman initially proposed a RCT of steroids versus placebo in pediatric septic shock but the project was put on hold because of lack of equipoise among physician staff at Network clinical sites. In response, Dr. Zimmerman designed a comprehensive prospective observational cohort study, the “Clinical Outcome Measures in Pediatric Sepsis Syndrome” (COMPASS), to better inform the study design process. COMPASS will describe the long-term health related quality of life in children surviving sepsis and develop and validate a composite outcome of “death + new disability”. The study is slated to begin in autumn, 2009. In preparation, the Network also completed a study of a simplified and faster methodology to measure free cortisol, comparing centrifugal ultrafiltration to equilibrium dialysis (37). This approach may allow clinically relevant turn-around times for measurement of free cortisol levels, which may be a better reflection of adrenal sufficiency (38–40). The study also obtained biologic samples to investigate various single nucleotide polymorphisms in genes regulating cortisol metabolism. Analysis of these data is ongoing.

Measuring Opioid Tolerance Induced by Fentanyl (or other opioids): The MOTIF Study

Provision of adequate pain relief and sedation in children is an important aspect of critical care. Sedation and analgesia present a conundrum, however, because these commonly used drugs become increasingly ineffective over time due to the development of tolerance (41,42). The flip side of tolerance, withdrawal, is also problematic as it may prolong mechanical ventilation, extend hospitalization, and necessitate a protracted weaning process (43,44). Defining the incidence of opioid tolerance, the risk factors for its development, and objective outcomes to measure tolerance is the focus of a prospective observational study designed by K.J.S. Anand. This ongoing study will provide the preliminary data to design a prospective clinical trial examining the effectiveness of low-dose opioid antagonists (e.g., naloxone) and NMDA agonists (e.g., ketamine) in preventing development of opioid tolerance in critically ill children. Data collection is expected to be complete by December 2009.

Mechanical Ventilation Decision Support

The determinants of ventilator-induced lung injury (VILI) remain to be fully defined but there is general consensus regarding the value of avoiding lung over-distention (45–47). The approach to mechanical ventilation across and even within PICUs is far from uniform (48), however, and likely results in poorer outcomes and compromises our ability to study therapeutic interventions in ventilated patients. Christopher Newth, in conjunction with the informatics staff at the University of Utah DCC and other members of the Network, has developed open loop decision support software to allow a more uniform approach to ventilator management. The software uses modifications of the rules and algorithms developed originally by the ARDS Network and is currently being tested in the Network in preparation for its use to study high frequency versus conventional ventilation in children with acute lung injury.

Therapeutic Hypothermia after Pediatric Cardiac Arrest (THAPCA)

Induced hypothermia has demonstrated efficacy after birth asphyxia in newborns (49–51) and cardiac arrest in adults (52–54) but few data exist in children. Frank Moler (University of Michigan) and J. Michael Dean (University of Utah) in collaboration with CPCCRN, PECARN (Pediatric Emergency Care Applied Research Network), and the Canadian Pilot Group have received NHLBI funding for the THAPCA Trial, two simultaneous multi-institutional randomized controlled trials of hypothermia after cardiac arrest in children (separate trials of in-hospital and out-of-hospital cardiac arrest). The THAPCA Trials were planned over a four-year period with NICHD R21 and R34 grant support (55,56). The University of Utah will act as the DCC and Kathleen Meert as the CPCCRN sponsoring PI. Eligible subjects for the study are children stabilized after documented cardiac arrest who have received chest compressions for at least two minutes. Subjects will be randomized within 6 hours of return of circulation and treated with moderate hypothermia (32–34 °C) versus controlled normothermia for 48 hours. All other treatments will be unchanged. The primary outcome for the six-year study will be survival with good neurobehavioral outcome 12 months after cardiac arrest.

Critical Asthma

Asthma is the most common chronic disease in childhood (57). Fatal asthma is relatively rare, but status asthmaticus is a frequent reason for PICU admission. The determinants of critical asthma, events surrounding fatal and near-fatal asthma attacks, and effective treatment are poorly characterized (58). The Network developed a working critical asthma group anticipating support in 2008 from the BPCA (Best Pharmaceuticals for Children Act) to accomplish three goals: (1) Review all asthma deaths and near fatal asthma admission in

the CPCCRN registry; (2) Describe the demographics, treatment, and outcomes of critical asthma in patients from the registry, identifying strategic therapeutic decision points that need further investigation; and (3) Develop a prospective cohort study that will determine sample size and appropriate outcomes measures, as well as refining identified decision points that might be appropriate for a future interventional trial.

Additional Papers Published from the Network

Network PIs are collaborating on a number of manuscripts that address common issues in Pediatric Critical Care. Brief descriptions of these manuscripts follow.

Weaning and Extubation Readiness in Pediatric Patients

Mechanical ventilation can be life-saving but is associated with a variety of potential complications, many of which become more likely with increasing time on the ventilator. While there has been much attention to optimal ventilator strategy during the acute phase of respiratory failure, separating from ventilator support by weaning and extubation has received little attention in the Pediatric literature. In this manuscript Christopher Newth and colleagues review the current state of the art regarding weaning and extubation in children and identify the unresolved issues. This paper has been published in *Pediatric Critical Care Medicine* (68).

Is Rescue Therapy Ethical in Randomized Controlled Trials?

This paper was initiated by a discussion regarding the ethics of allowing a “bail-out” or “rescue” for children potentially enrolled in Dr. Zimmerman’s proposed RCT of corticosteroids in sepsis. Richard Holubkov, a biostatistician and alternate PI for the Network DCC, and colleagues persuasively argue that while a “rescue” therapy component may be perceived as ethically desirable, the inconsistency of “rescue” therapy with full equipoise may itself raise significant ethical concerns. A “rescue” arm necessitates an increased sample size and, consequently, may expose more children to whatever risks are incurred by study participation. Additionally, a “rescue” component cannot definitively determine the beneficial or harmful effects of a treatment *per se*, but can only assess the effects of delayed versus immediate provision of the treatment. This paper has been accepted for publication in *Pediatric Critical Care Medicine* (69).

Prolonged use of Opioid Analgesia in Critically Ill Children

Analgesic regimens for children commonly include opioids because of their clinical utility in nearly all types of pain and critical illness (70,71). Critically ill children requiring mechanical ventilation and invasive monitoring are routinely treated with opioids for analgesia and sedation (71,72). Increasing use of opioid analgesics, however, often leads to the development of tolerance and withdrawal if the drugs are acutely discontinued (41–44,73,74). This review, authored by K.J.S. Anand and CPCCRN investigators, discusses the epidemiology and mechanisms of opioid tolerance and withdrawal, the underlying genetic, genomic, and cellular mechanisms, and novel approaches to avoid opioid tolerance and withdrawal. It suggests that understanding the mechanisms of opioid tolerance will help clinicians increase the effectiveness of currently available analgesics and reduce the incidence and severity of opiate withdrawal. This paper has been accepted for publication by *Pediatrics*.

Looking Towards the Future: Network Re-competition

The productivity of the Network over the first 5-year cycle (concluding November 30, 2009) enabled the NICHD to re-issue the RFAs for another 5-year funding cycle to provide up to

six to eight new or competing continuation awards (RFA 08-HD-0025; see http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-08-025.html), and for the DCC (RFA 08-HD-0027; see http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-08-027.html) (75,76). Both the CPCCRN and the DCC are funded through cooperative agreement award mechanisms (U10 and U01, respectively). In these agreements the PI retains primary responsibility for the planning and conduct of research, while the NICHD staff maintains substantial scientific and administrative involvement as a partner with the PIs, beyond the usual programmatic financial stewardship present in all extramural awards.

A Special Emphasis Panel (SEP) comprised of experts in the fields of pediatrics will review applications and submit summary statements and priority scores to NICHD. Selection criteria include both the scientific rigor of the research plan and the PI's and institution's ability to conduct and support multicenter pediatric critical care research. The NICHD funding plan considers factors including, but not limited to: priority scores; geographic location; ethnic, gender and racial diversity and nature of the pediatric critical care population available for study; PI expertise; evidence of PI research productivity; commitment of the institution to the conduct of research; and evidence of commitment to following children after PICU discharge. For the new funding cycle participating CPCCRN sites are required to designate a follow-up investigator who is both skilled and credentialed to perform detailed neurological, functional and developmental assessments. The capacity to follow children and capture data about their status for up to two years is central in the review of an applicant's qualifications for participation in the network.

The new funding cycle begins December 1, 2009, following second level review by the Advisory Council of NICHD at its October, 2009 session. During the transition from the original to the new funding cycle, it is anticipated that on-going projects will continue at existing CPCCRN sites and new network sites will initiate those projects as well. Subject accrual, data analysis, and dissemination of findings in the literature will be facilitated throughout the transition period in order to continue to meet the research goals of the network.

Summary and Conclusions

The NICHD CPCCRN was conceived as a means of improving the care of critically ill children through collaborative multi-institutional clinical and translational research. In the initial cycle of support years a number of studies have been initiated, some completed, and others are in development. Few of these studies could have been accomplished or considered without the collaboration of 7 excellent children's hospitals and the support of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). The Network remains committed to its stated goal "to initiate a multi-centered 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".

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