Multicenter Pediatric Emergency Medicine Research and Rhode Island

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ABSTRACT

Multicenter clinical research studies are often needed to address issues of generalizability, conditions with low incidence, adequate statistical power, and potential study bias. While pediatric research networks began work in the 1950s, and Rhode Island physicians have contributed to many of these studies, pediatric emergency medicine (PEM) collaboratives are relative newcomers. Since the mid-1990s, Rhode Island pediatricians have contributed to multicenter studies of diabetic ketoacidosis, bronchiolitis, asthma, quality of PEM care, meningitis, brief interventions for substance use disorders, point-of-care ultrasound, and pre-hospital triage protocols.

In 2011, Rhode Island Hospital joined the Pediatric Emergency Care Applied Research Network, the first federally funded pediatric emergency medicine network of its kind. Its mission is to perform high quality, high impact PEM research. Since joining the network, Rhode Island Hospital has quickly become a productive and valued member of the network, portending a bright future for multicenter PEM research in the Ocean State.

KEYWORDS: pediatric, multicenter, research, PECARN

THE NEED FOR MULTICENTER PEDIATRIC RESEARCH

High quality medical research must successfully address many challenges. Single-center studies frequently encounter problems with generalizability as patient, geographic, and socioeconomic factors frequently bias results. Such studies may also suffer from lack of statistical power, to either definitively answer a clinical question or provide estimates with reasonable statistical confidence. Pediatric research often faces the additional conundrums of conditions or outcomes with low incidence, a wide range of severity of illness or injury, and the ethical, legal and logistic considerations of obtaining assent and consent of minors and their parents. All of these factors complicate and pose barriers to rigorous pediatric studies.

Multicenter studies offer a potential solution. The benefits of multicenter trials include the ability to recruit a larger number of and more diverse participants from a variety of geographic locations, and the possibility of evaluating the effect of practice variation between sites. It is likely that genetic, ethnic, environmental, psychosocial, and cultural factors all make significant contributions to observed medical phenomena. Multicenter trials may be the only method for properly investigating these effects, and providing robust, generalizable clinical data.

The first national pediatric multicenter networks were formed by oncologists in the 1950s, rheumatologists in the 1970s, and neonatologists in the 1980s. To address research in primary care settings, regional pediatric research collaboratives formed in Rochester, NY, and Chicago, IL, in the 1970s and 1980s respectively, ultimately resulting in the formation of the PROS (Pediatric Research in Office Settings) by the American Academy of Pediatrics (AAP) in 1985.[1] Since their inception, Rhode Island pediatricians and investigators have contributed to numerous studies in the neonatology, hematology-oncology and PROS networks, and have recently begun to collaborate with critical care networks as well.[2,3]

Multicenter Pediatric Emergency Medicine Research

Beginning in the mid-1990s, members of the AAP's Section of Emergency Medicine formed the Pediatric Emergency Medicine Collaborative Research Committee (PEM-CRC), which has subsequently produced numerous multicenter studies, on broad ranging topics, from career satisfaction, diabetic ketoacidosis, infectious diseases, and cardiac arrhythmias, to appendicitis clinical prediction rules.[4-10] To further address the need for and challenges of high quality pediatric emergency medicine research, in 2001 the Emergency Medical Services for Children (EMSC) branch of the Maternal and Child Health Bureau of the Health Resources and Services Administration (HRSA) funded proposals to "demonstrate the value of an infrastructure or network…to conduct investigations on the efficacy of treatments,…including those preceding the arrival of children to the hospital." As a result of this request, the Pediatric Emergency Care Applied Research Network (PECARN) was born.[11,12]

Table 1.

PECARN Nodes and Sites	
GLEMSCRN **Great Lakes EMSC Research Network** • University of Michigan, Ann Arbor, MI • Children's Hospital of Michigan, Detroit, MI • Nationwide Children's Hospital, Columbus, OH	HOMERUN **Hospitals of the Midwest Emergency Research Node** • Cincinnati Children's Hospital, Cincinnati, OH • Washington University, St. Louis, MO • Children's Hospital of Wisconsin, Milwaukee, WI
PEM-NEWS **Pediatric Emergency Medicine-Northeast, West & South** • Children's Hospital of New York, New York, NY • Children's Hospital of Colorado, Denver, CO • Texas Children's Hospital, Houston, TX	PRIME **Pediatric Research in injuries and Medical Emergencies** • University of California, Davis, CA • Children's Hospital of Philadelphia, Philadelphia, PA • Primary Children's Medical Center, Salt Lake City, UT
PRIDENET **Pittsburgh, Rhode Island, Delaware Network** • Children's Hospital of Pittsburgh, Pittsburgh, PA • Hasbro Children's Hospital, Providence, RI • A.I. duPont Hospital for Children, Wilmington, DE	WBCARN **Washington, Boston, Chicago Applied Research Node** • Children's National Medical Center, Washington, DC • Children's Hospital of Boston, Boston, MA • Lurie Children's Hospital, Chicago, IL
CHaMP E-RNC **Charlotte, Houston, Milwaukee Prehospital EMS Research Node** • Milwaukee County EMS, Milwaukee, WI • Mecklenburg EMS Agency, Charlotte, NC • Houston Fire Department EMS, Houston, TX	

PECARN emergency departments (ED's) currently care for over 900,000 children and adolescents annually, with over-representation of minorities and underserved populations. Since its inception, PECARN has produced more than 150 publications, abstracts and presentations at national meetings.

PECARN's infrastructure funding has been renewed three times by HRSA. In the most recent funding cycle of 2011, PECARN reorganized to 18 major academic pediatric centers across the country, centered around 6 research "nodes," each consisting of 3 affiliated hospitals. An entirely new node was added, PRIDENET – the **P**ittsburgh, **R**hode **I**sland, and **De**laware **Net**work, marking Hasbro Children's Hospital and Brown University's entry into PECARN. Since joining PECARN, Hasbro Children's Hospital has quickly become a high performing site, consistently enrolling high percentages of eligible participants and contributing high quality data on these participants. The most recent addition to PECARN was a demonstration EMSC node in 2013.

The formation of the AAP's PEM-CRC and PECARN subsequently spawned similar organizations across the world, including PERC (Pediatric Emergency Research Canada),[13] PREDICT (Pediatric Research in Emergency Departments International Collaborative Australia and New Zealand),[14] and REPEM (Research in European Paediatric Emergency Medicine).[15] In 2009, these networks joined together to form the consortium of PERN, Pediatric Emergency Research Networks.[16,17] Together, PERN ED's care for over 2 million pediatric patients per year, in over 100 hospitals, in 4 of the 6 World Health Organization regions. They also recently published their first global pediatric emergency research study.[18]

While PECARN and other research networks offer the potential of an increased participant pool, multicenter networks face important challenges, including the possibility of variations in data collection, inter-rater reliability, protocol compliance, and the significant expense of maintaining such networks. Multicenter studies are complex and time-consuming undertakings, requiring painstaking preparation, detailed, comprehensive, and unambiguous study protocols, clearly delineated roles and responsibilities of study personnel, and coordinated IRB approval across multiple institutions. The success of networks hinge on all sites having adequately trained and committed research personnel, who collect and transmit study data in a timely and efficient manner.[1,19]

RHODE ISLAND'S CONTRIBUTION TO MULTICENTER PEDIATRIC EMERGENCY MEDICINE RESEARCH

Since joining PECARN, we have participated in 4 exciting studies, each of which has the potential to revolutionize care of children and adolescents.

RNA "Biosignatures" for Febrile Infants

Neonates with fever are at increased risk of serious bacterial infections (SBI), and routinely undergo invasive testing

of blood, urine, and cerebrospinal fluid. Because current laboratory testing strategies cannot rapidly or consistently distinguish which patients have bacterial or viral illnesses, many infants are admitted for 24-48 hours of observation. Assessing host response to infections may be an accurate, ground-breaking and novel method for determining the etiology of a febrile infant's fever.[20] Microarray analysis of very small amounts of blood, in which "biosignatures" of transcriptional leukocyte RNA may reliably differentiate between bacterial and viral pathogens.

Figure 2 is an example of such biosignatures.

Figure 2.

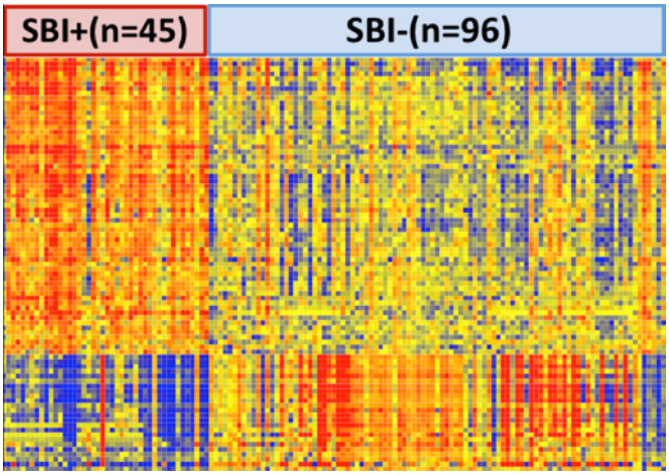

Image courtesy of Prashant Mahajan, MD, MPH, MBA

Each column represents an individual patient, each row represents a different leukocyte indicator gene. The red color signifies over-expression of a gene, while blue color indicates under-expression of that gene. As is easily seen in the picture, SBI-positive and SBI-negative patients appear to have very different biosignatures. Preliminary analyses (personal communication from study investigators) suggest that bacterial infections over-express inflammatory genes and under-express interleukin genes, while viral infections have the opposite pattern. If validated, this technology may dramatically alter how febrile neonates are evaluated and managed.

Diabetic Ketoacidosis and Cerebral Edema

Cerebral edema (CE) is a well known and the most feared complication of diabetic ketoacidosis (DKA).

Old studies suggested that intravenous (IV) fluids were the underlying cause of cerebral injury in DKA. However, DKA research from the last decade has shown that IV fluid administration is not associated with CE. Cerebral hypoperfusion and reperfusion injuries play a key role in DKA-related brain injury. A wide spectrum of CE is often present both before and during treatment for DKA. Neurologic symptoms can be present in the absence of radiologically detectable CE, and even mild DKA may result in long-term neurocognitive deficits.[21]

Based on these data and to address this vexing question, PECARN is currently investigating whether the type and rate of IV fluid administration affect both short- and long-term neurocognitive outcomes of DKA (National Institute of Child Health and Human Development, U01 HD062417). Utilizing a 2x2 factorial design, the study varies the amount of IV fluids given (10 vs 20 cc/kg initial bolus), the rate at which they are given (rapid deficit replacement over 36 hours vs slower replacement over 48 hours), and the type of IV fluid (0.45% vs 0.9% saline). The primary outcome of the study is the occurrence of Glasgow Coma Scale < 14 (15 being normal); the secondary outcomes are incidence of overt CE, and neurocognitive assessments while hospitalized and at 3 month follow-up. The study has a planned enrollment of 1,500 participants. When completed, this study will likely contribute significant, robust data towards answering the question of whether any of these IV fluid regimens either exacerbate or protect against DKA-related cerebral injury.

Figure 3. Diffusion weighted MRI, cytotoxic cerebral edema.

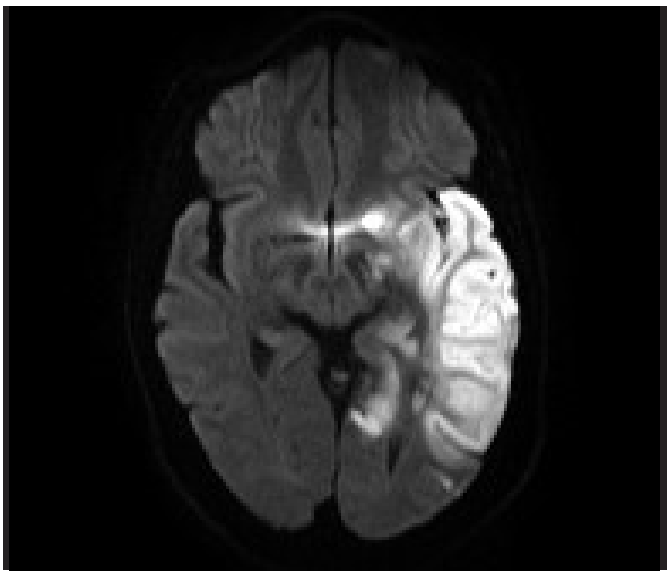

Image courtesy of Jerrold Boxerman, MD and Jeffrey Rogg, MD

PECARN Core Data Project

While many federal agencies collect epidemiologic data on emergency department visits, pediatric specific data has been lacking. To address this deficit, from 2002 to the present, PECARN has compiled data on all patient visits to participating ED's into a single database, the PECARN Core Data Project (PCDP). Using PCDP data, PECARN has been able to drill down into its specific epidemiologic database and perform more granular epidemiologic analyses as compared to other large database studies of pediatric ED visits, identifying patterns related to patient age (e.g., ED visits, hospital admission, and mortality) and the most common conditions for which patients sought care (i.e., infectious diseases, asthma, and mental health conditions).[22,23] Such data is important in helping inform institutions with needs assessments

and resource planning, providing a rigorous basis for epidemiologic reporting and research, as well as developing clinically and epidemiologically sensible diagnostic grouping systems for ED visits by children and adolescents.[24]

PECARN investigators currently seek to advance the use of clinical and epidemiologic data, by extracting more detailed information from electronic health records (Agency for Healthcare Research and Quality, R01 HS020270). The aims of this study are to identify variation in clinical performance and outcomes, with the ultimate goal of improving both patient and quality of care by identifying clinically relevant, evidence-based benchmarks and vastly improving the evaluation of healthcare delivery. If successful, the project would also represent a quantum leap forward in the abstraction of clinical data from electronic health records.

NIAAA Two-Question Screen

Alcohol use is a significant contributor to adolescent morbidity and mortality. It may result in long-term anatomic and neuropsychologic changes and is a strong predictor of adult alcohol use disorders. Given this public health burden, in 2011 the National Institute of Alcohol Abuse and Alcoholism (NIAAA) developed and published a practitioner's guide to assist pediatricians in screening for and intervening in adolescent alcohol use.[25] NIAAA recommends asking adolescents two simple, brief questions about their alcohol use and their friends' experiences with alcohol. NIAAA also believes that these two questions may also reliably predict risk of other substance use and problem behaviors.

The 2 questions as well as the NIAAA practitioner guide can both be downloaded for free from NIAAA at: http://www.niaaa.nih.gov/Publications/EducationTrainingMaterials/Pages/YouthGuide.aspx

To further validate the NIAAA two-question screen and to investigate whether it has predictive ability for other adolescent risky behaviors, shortly after publishing their practitioner's guide, NIAAA released a funding opportunity (RFA-AA-12-008) to study these questions. Utilizing the PECARN network, James Linakis PhD, MD, and Anthony Spirito, PhD, researchers at Rhode Island Hospital and Brown University respectively, received one of these awards (NIAAA, R01 AA021900). The NIAAA two-question screen is currently being tested in 16 PECARN EDs, with a planned study enrollment of 5,000 adolescents, 1,600 of whom will be followed for 2 years. This study will capture a broad cross-section of U.S. adolescents and will generate very robust and generalizable data in terms of age, gender, race and ethnicity, level of alcohol use, and geographic diversity. If valid screening tools are identified, this study has the potential to offer pediatric practitioners a rapid and efficient method for identifying high-risk adolescents.

CONCLUSION

In just a few short years, pediatric emergency medicine research in Rhode Island has significantly grown. Diverse studies, with the potential to dramatically change and improve clinical practices, are now being performed in our state. Joining the PECARN network is an exciting opportunity to continue this growth in research productivity, as well as for new collaborative studies.

References

1. Wasserman R., et al. The APA and the rise of pediatric generalist network research. *Acad Pediatr*. 2011;11(3):195-204.
2. Nishisaki A., et al. A National Emergency Airway Registry for children: landscape of tracheal intubation in 15 PICUs. *Crit Care Med*. 2013;41(3)874-85.
3. Sanders RC, Jr., et al. Level of trainee and tracheal intubation outcomes. *Pediatrics*. 2013;131(3):e821-8.
4. Glaser N, et al. Risk factors for cerebral edema in children with diabetic ketoacidosis. The Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. *N Engl J Med*. 2001;344(4):264-9.
5. Losek JD, et al. Adenosine and pediatric supraventricular tachycardia in the emergency department: multicenter study and review. *Ann Emerg Med*. 1999;33(2)185-91.
6. Losek JD. Characteristics, workload, and job satisfaction of attending physicians from pediatric emergency medicine fellowship programs. Pediatric Emergency Medicine Collaborative Research Committee. *Pediatr Emerg Care*. 1994;10(5):256-9.
7. Dowd MD, Krug S. Pediatric blunt cardiac injury: epidemiology, clinical features, and diagnosis. Pediatric Emergency Medicine Collaborative Research Committee: Working Group on Blunt Cardiac Injury. *J Trauma*. 1996;40(1):61-7.
8. Mittal MK, et al. Performance of ultrasound in the diagnosis of appendicitis in children in a multicenter cohort. *Acad Emerg Med*. 2013;20(7):697-702.
9. Kharbanda AB, et al. Validation and refinement of a prediction rule to identify children at low risk for acute appendicitis. *Arch Pediatr Adolesc Med*. 2012;166(8):738-44.
10. Schnadower D, et al. Febrile infants with urinary tract infections at very low risk for adverse events and bacteremia. *Pediatrics*. 2010;126(6):1074-83.
11. The Pediatric Emergency Care Applied Research Network (PECARN): rationale, development, and first steps. *Pediatr Emerg Care*. 2003;19(3):185-93.
12. The Pediatric Emergency Care Applied Research Network (PECARN). [cited 2013 October 16]; Available from: www.pecarn.org.
13. Pediatric Emergency Research Canada (PERC). [cited 2013 October 16]; Available from: perc.srv.ualberta.ca.
14. Paediatric Research in Emergency Departmens International Collaborative (PREDICT). [cited 2013 October 16]; Available from: http://pems-aunz.org/PREDICT/.
15. Research in European Paediatric Emergency Medicine (REPEM). [cited 2016 October 16]; Available from: http://www.pemdatabase.org/REPEM.html.
16. Pediatric Emergency Research Networks (PERN). [cited 2013 October 16]; Available from: http://pems-aunz.org/PERN/Home.php.

17. Klassen TP, et al. Pediatric emergency research networks: a global initiative in pediatric emergency medicine. *Pediatr Emerg Care*. 2010;26(8):541-3.
18. Dalziel SR, et al. Predictors of severe H1N1 infection in children presenting within Pediatric Emergency Research Networks (PERN): retrospective case-control study. *BMJ*. 2013;347:f4836.
19. Aisen ML, Schafer K. Basic Principles of Setting Up Multicenter Trials. *Neurorehabilitation and Neural Repair*. 1997;11(3):185-8.
20. Mahajan P, Ramilo O, Kuppermann N. The future possibilities of diagnostic testing for the evaluation of febrile infants. *JAMA Pediatr*. 2013;167(10):888-98.
21. Glaser NS, et al. Pediatric diabetic ketoacidosis, fluid therapy, and cerebral injury: the design of a factorial randomized controlled trial. *Pediatr Diabetes*. 2013;14(6):435-46.
22. Alpern ER, et al. Epidemiology of a pediatric emergency medicine research network: the PECARN Core Data Project. *Pediatr Emerg Care*. 2006;22(10):689-99.
23. Mahajan P, et al. Epidemiology of psychiatric-related visits to emergency departments in a multicenter collaborative research pediatric network. *Pediatr Emerg Care*. 2009; 25(11):715-20.
24. Alessandrini EA, et al. A new diagnosis grouping system for child emergency department visits. Acad Emerg Med. 2010;17(2):204-13.
25. National Institute of Alcohol Abuse and Alcoholism. Alcohol Screening and Brief Intervention for Youth: A Practitioner's Guide. 2011. Washington, D.C.

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Disclosures
None

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