Translating Best Evidence into Best Care

EDITOR'S NOTE: Studies for this column are identified using the Clinical Queries feature of PubMed, "hand" searching *JAMA*, *JAMA Pediatrics*, *Pediatrics*, *The Journal of Pediatrics*, and *The New England Journal of Medicine*, and from customized EvidenceUpdates alerts.

EBM PEARL: MULTIPLE LOGISTIC REGRESSION (MLR): Researchers use MLR to identify characteristics that may affect an outcome of interest. Cain et al (below) employed MLR to assess the influence of various patient characteristics on whether or not a child presenting with headaches received neuroimaging (the outcome of interest). In MLR language, neuroimaging is the dependent variable and is binary (yes/no). The patient characteristics included white race, no headache history, no similar headaches in the past, vision changes, speech difficulty, weakness, altered mental status, and others. The initial step was to perform univariate logistic regression, testing the effect of each individual patient characteristic on whether the child received neuroimaging. Those patient characteristics (that met certain statistical criteria) that were statistically-significantly associated with receiving neuroimaging were then evaluated with MLR. This second step evaluated each of the chosen statistically-significant patient characteristics in relation to all the others. Some of the characteristics ended up not statistically significant in this analysis due to strong correlation (overlap) among 2 or more characteristics. The result of the MLR analysis was a smaller set of independently associated, statistically-significant patient characteristics that affected the decision to image the patient: any abnormal neurologic finding, no similar headaches in the past, and white race. These were the primary findings of the Cain et al study (commentary below).

CRITICAL STATISTICAL DISTINCTION PEARL: STATISTICAL TESTS FOR BINARY VS CONTINUOUS DATA: EBM learners of all levels may not realize that many statistical terms and tests use only one type of data. An important "critical distinction" in EBM is the practical use of binary and continuous data. Here are 5 helpful hints: 1) Examples of binary data include: headaches present (yes/no) and headaches improved (>50%/<50%). 2) Examples of continuous data include blood pressure and age measures (mean +/− standard deviation). 3) Statistics that employ binary data include likelihood ratios, sensitivity, specificity, absolute risk reduction, relative risk, odds ratio and the Chi square test. 4) Statistics that employ continuous data include ANOVA and paired and independent t-tests. 5) Finally, 95% confidence intervals may be used for both types of data.

—Jordan Hupert, MD

Patient characteristics and neuroimaging for headache in the ED

Cain MR, Arkilo D, Linabery AM, Kharbanda AB. Emergency Department Use of Neuroimaging in Children and Adolescents Presenting with Headache. *J Pediatr* 2018;201:196-201.

Question Among children presenting to the emergency department (ED) with headache, what is the association of patient characteristics and neuroimaging?

Design Prospective cohort.

Setting Two pediatric EDs in Minnesota.

Participants 294 children, 6-18 years old, with headache.

Intervention Patient characteristics.

Outcomes Neuroimaging (CT or MRI).

Main Results 0.7% (95% CI, 0.1%-2.4%) and 3.8% (95% CI, 0.5%-13%) of all and of the 53 patients undergoing neuroimaging, respectively, demonstrated clinically important intracranial findings. Abnormal neurologic findings, new-type headache, and white race were all associated with undergoing neuroimaging.

Conclusions The low clinically-important-intracranial-finding rate suggests the need for more refined algorithm development based on large study populations. Bias in the odds of receiving neuroimaging should be addressed.

Commentary Cain et al bring attention to the public health problem at hand: a large proportion of children with headaches are undergoing unnecessary neuroimaging and are exposed to the risks of morbidity and mortality associated with CT scans and MRIs. Conducted in 2 EDs, their findings reflect the high rate of neuroimaging in children with non-traumatic headaches described both nationally (36%) and at our own center (33%), the latter in which we described a similarly low prevalence of emergent intracranial abnormalities (1%).[1,2] The risk factors identified for receiving ED neuroimaging in children with headaches are important when looking to change behavior in clinicians. However, as noted by the authors, the million-dollar question remains: which risk factors should be used to determine if a child with headache requires ED neuroimaging? Similar to other studies preceding Cain et al, the number of outcomes is too small to adequately answer this question. Larger prospective studies are necessary to move

beyond identifying risk factors for receiving ED neuroimaging to identifying risk factors associated with emergent intracranial abnormalities. These studies should develop clinical prediction rules or risk stratification models that can serve as the basis for standardizing and optimizing the evaluation of children with headaches, with the hope of preventing further harm associated with unnecessary ED neuroimaging.

Daniel S. Tsze, MD
Columbia University College of Physicians and Surgeons
New York, New York

References

1. Sheridan DC, Meckler GD, Spiro DM, Koch TK, Hansen ML. Diagnostic testing and treatment of pediatric headache in the emergency department. J Pediatr 2013;163:1634-7.
2. Tsze DS, Ochs JB, Gonzalez AE, Dayan PS. Red flag findings in children with headaches: prevalence and association with emergency department neuroimaging. Cephalalgia 2018;96:333102418781814.

Neither fluid rate nor sodium content affect neurocognitive outcomes in DKA

Kuppermann N, Ghetti S, Schunk JE, Stoner MJ, Rewers A, McManemy JK. Clinical Trial of Fluid Infusion Rates for Pediatric Diabetic Ketoacidosis. *N Engl J Med* 2018;378:2275-87.

Question Among children with diabetic ketoacidosis (DKA) what is the effect of intravenous fluid administration (IVF) rate and sodium content on the incidence of neurocognitive injury?

Design 2 × 2 factorial, randomized controlled trial.

Setting 13 emergency departments in the Pediatric Emergency Care Applied Research Network (PECARN).

Participants 1255 children (0-18 years) with 1389 DKA episodes.

Intervention Fast vs slow IVF administration rate and 0.9% vs 0.45% normal saline.

Outcomes Primary outcome: 2 consecutive Glasgow Coma Scale (GCS) scores of <14 among children presenting with scores of 14 or 15. Secondary outcome: clinically apparent brain injury.

Main Results There were no differences in any of the neurocognitive outcomes.

Conclusions Neither fluid rate nor salinity affected neurocognitive outcomes in DKA.

Commentary Thirty years ago, it was suggested that fluid rates exceeding 4L/meter^2/24h increased the risk of cerebral edema.[1] A potential causal association between the rate or sodium chloride content of IVF administration for the treatment of DKA and the development of DKA-related brain injury (cerebral edema) continues to be controversial.[2] The PECARN DKA FLUID Study Group conducted a 13-center RCT in children with DKA comparing fluid with 0.9% sodium chloride vs 0.45% sodium chloride. Each was infused at either a slower rate (even fluid replacement over 48 hours) or a faster rate (half the deficit replaced in 12 hours and the remainder over the subsequent 24 hours). No significant differences were observed in the frequency of either altered mental status or clinically apparent brain injury in any of the treatment arms, and long-term neurocognitive outcomes were similar in all groups. It is also notable that in the subgroups of patients with more severe DKA, the percentage of episodes in which the GCS score declined to below 14 and the percentage of episodes with clinically confirmed apparent brain injury did not differ significantly among the groups. Edema may be a consequence rather than the cause of brain injury, and other mechanisms, in particular ischemia-reperfusion injury and neuroinflammation resulting in blood-brain barrier dysfunction, need to be explored.[2,3] This study shows that clinicians should not unnecessarily restrict fluid administration if clinical signs suggest the need for circulatory volume expansion. Rapid overhydration should be avoided; however, there is a risk that unduly cautious fluid resuscitation might prolong the cytotoxic effects of dehydration and acidosis. It is notable that impaired brain function occurred predominantly in patients who had more severe acidosis and a lower pCO_2 level, which suggests that such patients require even more careful clinical and biochemical monitoring.

Joseph Wolfsdorf, MB, BCh
Boston Children's Hospital
Boston, Massachusetts

References

1. Duck SC, Wyatt DT. Factors associated with brain herniation in the treatment of diabetic ketoacidosis. J Pediatr 1988;113:10-4.
2. Wolfsdorf JI, Glaser N, Agus M, Fritsch M, Hanas R, Rewers A, et al. ISPAD Clinical Practice Consensus Guidelines 2018: diabetic ketoacidosis and the hyperglycemic hyperosmolar state. Pediatr Diabetes 2018;19(Suppl 27):155-77.
3. Glaser N. Cerebral injury and cerebral edema in children with diabetic ketoacidosis: could cerebral ischemia and reperfusion injury be involved? Pediatr Diabetes 2009;10:534-41.

2-6 years-of-age is the period associated with greatest BMI acceleration among obese adolescents

Geserick M, Vogel M, Gausche R, Lipek T, Spielau U, Keller E, et al. Acceleration of BMI in Early Childhood and Risk of Sustained Obesity. *N Engl J Med* 2018;379:1303-12.

Question Among children and adolescents, what is the longitudinal, year-specific association of BMI in childhood with BMI in adolescence?

Design Retrospective and prospective secondary analysis of the CrescNet German patient registry.

Setting Germany.

Participants Sample of 51 505 children with longitudinal anthropometric data in childhood (0-14 years) and adolescence (15-18 years).

Intervention BMI progression in childhood.

Outcomes Year-specific association of BMI's in childhood and adolescence.

Main Results Most adolescents with normal weight always had a normal weight. Ninety percent of obese 3-year-olds were overweight or obese in adolescence. The greatest BMI acceleration occurred between 2-6 years of age.

Conclusions Obesity at a very young age is associated with obesity in adolescence, with 2-6 years of age being the period of greatest weight gain.

Commentary This study provides empirical data on growth trajectories from infancy to adolescence and finds that early childhood may be a critical period for excess weight gain. Although it provides important information on the dynamics of growth trajectories, it is not clear how these findings based on retrospective data should best be used to inform practice for today's children. Specific obesogenic factors were not identified in the study, and given the many changes in environmental influences in recent years, the causes of excess weight gain among study participants from previous cohorts may not be the same as for current children. In addition, focusing on a "high-risk" age group may not translate into an effective long-term prevention strategy as efforts to prevent excess weight in this age group may simply defer weight gain to later ages. Sustained obesity prevention efforts across the life course may be more effective than trying to intervene in "critical periods." Further work to identify the underlying factors which contribute to excess weight gain would help to contextualize results from retrospective studies for today's children and help design specific interventions.

Zachary J. Ward, MPH
Harvard T.H. Chan School of Public Health
Boston, Massachusetts

Maternal voice smoke alarms outperform tone alarms in waking grammar-school-age children

Smith GA, Chounthirath T, Splaingard M. Effectiveness of a Voice Smoke Alarm with the Child's Name for Sleeping Children: A Randomized Trial. *J Pediatr*;205:250-6.

Question Among grammar-school-age children, what is the efficacy of a maternal voice smoke alarm (using the child's name, escape instructions, or both), compared with a tone alarm, in waking and escaping rates?

Design Randomized, nonblinded, repeated measures design.

Setting Research setting with a replica residential bedroom, Columbus, Ohio.

Participants Children 5-12 years old.

Intervention Voice vs tone smoke alarm.

Outcomes Waking and escaping rates.

Main Results The median times to awaken was 156.0 (6.0->300) seconds for the tone alarm and 2.0 (1.0-~6.0) seconds the voice alarms. The absolute risk reduction for voice compared with tone was 37.5% (95% CI, 29.0%-46.0%); the number needed to treat was 3 (95% CI, 3-4). Similar results were noted for waking and completing a simulated escape procedure.

Conclusions A maternal voice smoke alarm outperformed a tone alarm.

Commentary The prevention of residential fire deaths among school-aged children has been hindered because children at that age usually do not wake up to typical high frequency smoke alarms. Since these children can participate in their own escape from a house fire, finding an alarm type that is effective in waking them up could significantly improve their chances of successful escape. Smith et al report a follow up to their previous smaller trial, which in 2006 showed significant promise of a smoke alarm that used maternal voice rather than a tone.[1] In the current study of 176 children aged 5-12 years who slept in a research setting to mimic a residential environment, the maternal voice alarm dramatically outperformed the traditional tone alarm. With the maternal voice alarm, a far greater proportion of children in Stage 4 sleep woke up, woke up quicker, and succeeded in a simulated escape compared with the tone alarm. This is an advance that has real potential to save children's lives. This work would be furthered by careful evaluation of whether any voice works this well or if the child's mother's voice is key. If each family has to record their own voice alarm, this would add cost and might not be as widely accepted. The voice alarm should also be compared with the low frequency (520-Hz square wave) tone alarm adopted as the national standard in 2014.[2]

Kyran Quinlan, MD, MPH
Rush University Medical Center
Chicago, Illinois

References

1. Smith GA, Splaingard M, Hayes JR, Xiang H. Comparison of a personalized parent voice smoke alarm with a conventional residential tone smoke alarm for awakening children. Pediatrics 2006;118:1623-32.
2. National Fire Protection Association. NFPA 72: national fire alarm and signaling code. Quincy (MA): National Fire Protection Association; 2016.

Minitablets may be an acceptable alternative to liquid in infants and young children

Klingmann V, Linderskamp H, Meissner T, Mayatepek E, Moeltner A, Breitkreutz J, et al. Acceptability of Multiple Uncoated Minitablets in Infants and Toddlers: A Randomized Controlled Trial. *J Pediatr* 2018;201:202-7.

Question Among infants and toddlers/young children, how do minitablet placebos compare with liquid placebos, in acceptability and swallowability?

Design Open, randomized, single dose, 3-way cross-over design.

Setting A single center in Dusseldorf, Germany.

Participants Infants (6-23 months) and toddlers/young children (2-5 years).

Intervention Minitablet (25 and 100 minitablets in infants, 100 and 400 in toddlers/young children) vs liquid placebos.

Outcomes Acceptability and swallowability.

Main Results Among infants, both 25 and 100 minitablets were statistically superior to liquid for both acceptability and swallowability. In toddlers/young children acceptability was noninferior for 400 minitablets (but not 100) compared with liquid; swallowability was noninferior for 100 but not 400 minitablets compared with liquid.

Conclusions Minitablets are a superior alternative to liquid in infants. In older children, 400 minitablets are an acceptable alternative to liquid.

Commentary Acceptability of minitablets in children is important to those working in pharmaceutical development to ensure medicines meet the needs of patients. Previous work showed that tablets are superior to alternative oral formulations in children aged 1-4 years.[1] Klingmann et al provide evidence that multiple minitablets (up to 400) are accepted by children aged 2-5 years. The study is limited by ethical requirements to include only children who are able to swallow and are compliant and willing to accept the study procedures both of which may introduce bias in study outcomes. Reluctance to use solid dosage forms is often attributed to risks associated with choking yet no deglutition issues were detected with minitablets in a total of 372 participants. Taste is not an issue for placebo minitablets, which may not be valid for a commercial product. Future work should focus on the acceptability of commercial minitablets, with the associated hurdles associated with a real pediatric population and a real drug product.

Hannah Batchelor, BSc, PhD
University of Birmingham
Birmingham, United Kingdom

Reference

1. Van Riet-Nales DA, De Neef BJ, Schobben AFAM, Ferreira JA, Egberts TCG, Rademaker CMA. Acceptability of different oral formulations in infants and preschool children. Arch Dis Child 2013;98:725-31.