Current Best Evidence

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 EvidenceAlerts.

EBM PEARL: ALLOCATION CONCEALMENT: Randomized patient allocation to treatment groups reduces selection bias and is a key component in the proper conduct of a therapeutic trial. Properly generated random number generation for treatment allocation is insufficient. Allocation itself requires vigilance. The randomization process is corrupted when physicians or others involved in recruiting patients can detect the next patient's group assignment. Randomized trials with poor allocation concealment tend to yield larger effect estimates. Allocation concealment procedures vary. The most sophisticated utilize centrally located, independent randomization processes with strict concealment procedures, where the researchers call for the next assignment after providing patient information. A less sophisticated approach, but still adequate, employs the SNOSE — sequentially numbered, opaque, sealed envelope — method. This method also employs carbon paper that transfers required patient information written onto the allocation envelope, prior to opening the envelop, to the group assignment card inside. This is a common (and less expensive) method typically employed in small to modest-size randomized trials. When reading a randomized therapeutic trial article, look for the randomization concealment process description in the Methods section. The Manley et al study, discussed below, describes their concealment process employing the SNOSE method.

CRITICAL STATISTICAL DISTINCTION PEARL: SUPERIORITY AND NONINFERIORITY: Therapeutic trials of new or non-standard treatments may evaluate statistical significance or evaluate noninferiority (clinical equivalence) compared with standard therapy or placebo. The distinction between testing for improved clinical efficacy and for testing for clinical equivalence often lays in the treatment effect's confidence-interval interpretation. For example, in the article by Manley et al discussed below, the authors wished to evaluate whether high-flow nasal canula (HFNC) was clinically equivalent (noninferior) to nasal continuous positive airway pressure (CPAP), as HFNC is easier to use and readily available in non-NICU-level nurseries. They decided that the upper limit of equivalence between the 2 treatments would be a 10% difference between the failure rates of HFNC and nasal CPAP. The study demonstrated a failure rate difference of 10.3% (95% CI, 5.2% - 15.4%). Interestingly, although the failure rate essentially met the nonequivalence upper limit (10%), the 95% CI crossed the study-researcher-defined 10% level for clinical insignificance. The issue in noninferiority for this trial was not whether nasal CPAP conveyed a *statistically* significant benefit compared with HFNC — it certainly did (if it did not, the 95% CI would cross zero). This issue was whether the trial would demonstrate that HFNC was not *clinically* significantly worse (noninferior), and the trial could not demonstrate that, as the upper limit of the 95% CI crossed 10%, the authors' pre-defined noninferiority threshold.

—Jordan Hupert, MD

High-flow nasal canula not noninferior to nasal CPAP

Manley BJ, Arnolda GRB, Wright IMR, Owen LS, Foster JP, Huang L, et al. Nasal High-Flow Therapy for Newborn Infants in Special Care Nurseries. *N Engl J Med* 2019;380:2031-40.

Question Among neonates admitted to special care nurseries (a nontertiary-care nursery), is high-flow nasal canula (HFNC) noninferior, compared with nasal continuous positive airway pressure (CPAP), in preventing treatment failure?

Design Multicenter, randomized, controlled noninferiority trial.

Setting Special care nurseries in Australia.

Participants Neonates, <24 hours old and ≥31 weeks' gestation requiring respiratory support.

Intervention High-flow nasal canula (HFNC) vs nasal CPAP.

Outcomes Primary outcome: treatment failure within 72 hours after randomization. Treatment failure was defined as a fraction of inspired oxygen of "0.4 or higher for more than 1 hour to maintain target oxygen saturation levels of 91 to 95%; a pH of less than 7.2 plus a partial pressure of carbon dioxide greater than 60 mm Hg in 2 samples of arterial or capillary blood obtained at least 1 hour after commencement of the assigned treatment and obtained 1 hour apart; or 2 or more episodes of apnea for which positive-pressure ventilation was indicated within a 24-hour period or 6 or more episodes for which any intervention was indicated within a 6-

hour period," or urgent endotracheal intubation or transfer to an NICU. Noninferiority was defined as <10% difference in outcomes.

Main Results Seventy-eight of 381 vs 38 of 373 infants in the HFNC vs CPAP groups, respectively, experienced treatment failure. Absolute risk reduction, 10.3% (95% CI, 5.2% - 15.4%).

Conclusions HFNC was not noninferior to nasal CPAP.

Commentary In this multicenter, randomized, noninferiority trial, Manley et al investigated the possible role of HFNC therapy compared with nasal CPAP as the primary respiratory support for newborn infants with early respiratory distress in nontertiary special care nurseries. In the special care nursery setting, due to its simpler interface, HFNC is perceived as easier to use by medical and nursing specialists. Despite their data suggesting that CPAP was superior, HFNC therapy was successful in approximately 80% of infants and the clinical interpretation of these results may vary among different centers with different skill sets and other important variables beyond non invasive ventilation techniques. HFNC therapy may facilitate feeding and parental bonding and benefit the overall health status of the premature infant. Further multicenter, randomized trials evaluating the effect of HFNC on nutrition and growth are needed to better identify the most suitable non invasive respiratory technique for preterm infants with RDS.[1]

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1. Cresi F, Maggiora E, Borgione SM, Spada E, Coscia A, Bertino E, et al. Enteral Nutrition Tolerance and Respiratory Support (ENTARES) Study in preterm infants: study protocol for a randomized controlled trial. Trials 2019;20:67.

A rebound hyperbilirubinemia prediction rule

Chang PW, Newman TB. A Simpler Prediction Rule for Rebound Hyperbilirubinemia. *Pediatrics* 2019;144. pii: e20183712.

Question Among neonates completing phototherapy for hyperbilirubinemia, what is the probability, within 72 hours from completion, of a rebound total serum bilirubin (TSB) level reaching a new phototherapy threshold?

Design Retrospective cohort.

Setting Seventeen Kaiser Permanente hospitals.

Participants 7048 infants ≥35 weeks' gestational age (GA).

Intervention A 2-variable (GA and the starting threshold–ending TSB difference) rebound bilirubin prediction model.

Outcomes Probability of the TSB after phototherapy stopped 2 points below treatment threshold reaching the phototherapy threshold within 72 hours (defined as rebound).

Main Results 4.6% of infants had rebound. The model demonstrated a 2.5% rebound probability for infants ≥38 weeks' gestational age (stopping phototherapy at 2 mg/dL below the starting threshold) and 10.2% for infants <38 weeks' GA. For infants <38 weeks' gestation, phototherapy would need to be stopped at 5.5 mg/dL below the starting threshold to have a rebound probability (2.6%) similar to that of infants ≥38 weeks' GA.

Conclusions Rebound hyperbilirubinemia can be predicted by a 2-variable model. Patients <38 weeks' GA may require a longer phototherapy time due to a higher rebound risk.

Commentary Using the same cohort they used in their 2017 study,[1] Chang and Newman now find that a more parsimonious 2-variable (versus a 3-variable) model and a simpler equation, achieves similar accuracy in the prediction of rebound hyperbilirubinemia—a result that should please every newborn clinician. The clinical utility of these studies cannot be overemphasized. For the first time we can make an informed decision about whether to discontinue phototherapy and discharge the infant (assuming adequate follow-up) or continue the treatment to drive the bilirubin down and decrease the rebound risk, but prolong the hospital stay. The equation for determining the rebound score, Score = −4.3 X [starting threshold bilirubin – ending TSB] if GA is ≥38 weeks and 15.5 – 4.3 X [starting threshold bilirubin – ending TSB]) if GA is <38 weeks. I do wish that the authors had placed a parenthesis in front of the −4.3 so that it would be perfectly clear that the multiplication precedes the subtraction or (rarely) the addition. I recognize that this only applies to those of us not familiar with the mathematical convention that multiplication takes precedence over addition or subtraction, but a quick survey of my colleagues confirms that there are others similarly ignorant. This equation may, therefore, confuse some readers. The probability of rebound hyperbilirubinemia is determined by applying the calculated Score to the probability curve (see Figure 2 in the article). It must also be emphasized that this prediction rule currently applies only to infants who are <5 days old at the time of phototherapy and does not apply to those receiving their second exposure to phototherapy.

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Reference

1. Chang PW, Kuzniewicz MW, McCulloch C, Newman TB. A clinical prediction rule for rebound hyperbilirubinemia following inpatient phototherapy. Pediatrics 2017;139:e20162896.

Low-value radiographic imaging apparently less employed in Canada vs US emergency departments

Cohen E, Rodean J, Diong C, Hall M, Freedman, Aronson PL, et al. Low-Value Diagnostic Imaging Use in the Pediatric Emergency Department in the United States and Canada. *JAMA Pediatr* 2019:e191439.

Question Among pediatric and adolescent patients presenting to the ED, what is the comparative use of low-value imaging in Ontario, Canada, compared with the US?

Design Analysis from administrative health databases, 2006 - 2016.

Setting Four pediatric EDs in Ontario and 26 in the US.

Participants Patients ≤18 years discharged from an ED for diagnoses in which imaging is not routinely recommended.

Intervention Low-value imaging in Ontario and the US.

Outcomes Overall and low-value imaging rates.

Main Results Ontario had lower overall rates compared with the US for head computed tomography (CT), chest, and abdominal radiographs: rate differences, 2.2%, 3.9%, 12.2%, respectively (all $P < .01$). Low-value imaging was lower in Ontario for radiographs for constipation and abdominal pain, and CT of the head for concussion, rate differences: 23.7% (95% CI, 23.2% 24.3%), 20.6% (95% CI, 20.3% - 21.0%) and 22.9% (95% CI, 22.3% - 23.4%), respectively. Post-ED adverse outcomes were similar.

Conclusions Ontario EDs employ less low-value imaging compared with US EDs with similar post-ED adverse outcomes.

Commentary We should dwell on the key limitation here inherent to using diagnosis codes to measure ED low-value imaging. In contrast to the outpatient setting, ED visit coding is done at the conclusion of diagnostic imaging. If a radiograph of the chest was ordered to evaluate for pneumonia but the image ruled it out, then the ED clinician might code bronchiolitis or asthma. This image would be classified as "low-value," regardless of the pre-test probability of pneumonia. This problem is mitigated by focusing on trends and relative differences between the countries, but we should be cautious about accepting the absolute values of low-value imaging. There is little contention over whether low-value imaging in the US could safely be reduced—the real question is how. Several trends in the article are not explained by mostly static differences in payment and malpractice liability systems: 1) in some years, several low-value imaging rates became higher in Ontario; 2) some US low-value imaging rates fell by one-half over time, and these trends were mirrored in Ontario to a lesser degree; and 3) some low-value ultrasound and magnetic resonance imaging in Ontario increased substantially. Further work should be done to understand some of these other drivers of low-value imaging.

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Oral health problems associated with worse academic performance

Guarnizo-Herreño CC, Lyu W, Wehby GL. Children's Oral Health and Academic Performance: Evidence of a Persisting Relationship Over the Last Decade in the United States. *J Pediatr* 2019;209:183-9.e2.

Question Among school-age children, what is the association of oral health problems and academic performance?

Design Data analysis from the 2016-2017 National Survey of Children's Health.

Setting US.

Participants 45 711 children, 6-17 years old.

Intervention Oral health status.

Outcomes Academic performance (school report that the child had problems at school during the past year and the number of school days missed due to health issues).

Main Results Adjusted (demographic, socioeconomic, and health characteristics and state effects) ORs demonstrated significant associations between oral health problems and academic performance: reported problems at school, OR 1.56 (95% CI 1.32-1.85), at least 1 school day missed, OR 1.54 (95% CI 1.28-1.85), and more than 3 days missed, OR 1.39 (95% CI 1.20-1.61).

Conclusions Oral health problems in children is correlated with worse academic performance.

Commentary Despite a decade of advances in oral health prevention and treatment, strong associations between poor oral health and worse academic performance in children persist. The analysis conducted by Guamizo-Herreño et al demonstrates this is consistent across a range of factors including race/ethnicity, income, insurance type, and sex. The lack of variation by factors that are thought to modify both oral health and school performance behaviors raises interesting questions. Perhaps the observed association between oral health status and school performance is driven by the oral health condition itself. This argument is

strengthened by data demonstrating worse school performance with more oral pain. However, the association could also be related to common behaviors or conditions that predispose to worse outcomes in many areas. Oral health is influenced by individual genetics, child and family behaviors, and a range of family- and community-level influences.[1] Similar influences drive school performance.[2] More work is needed to better understand these important public health issues.

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Foreign body ingestion may be increasing in the US

Orsagh-Yentis D, McAdams RJ, Roberts KJ, McKenzie LB. Foreign-Body Ingestions of Young Children Treated in US Emergency Departments: 1995-2015. *Pediatrics* 2019;143. pii: e20181988.

Question Among children presenting to an emergency department (ED), how has the foreign body ingestion (FBI) rate varied over time?

Design Retrospective data analysis from the National Electronic Injury Surveillance System.

Setting US EDs.

Participants Children <6 years old who ingested a foreign body.

Intervention Presentation to an ED with complaint of FBI.

Outcomes FBI rates over time.

Main Results FBI rates increased from 9.5 to 18 per 10 000 in 1995 and 2015, respectively ($P < .001$). Coins were most common (61.7%), and button batteries were the most commonly ingested battery (85.9%).

Conclusions The FBI ingestion rate in US EDs has increased 91.5% over the 20-year period 1995-2015.

Commentary Orsagh-Yentis et al highlight a common problem among children presenting to EDs worldwide. This well-designed and executed study describes the epidemiology of FBI among children less than 6 years of age who were treated in US emergency departments from 1995 to 2015. Overall, the findings are reassuring for parents of children who accidentally ingest foreign bodies, suggesting that the vast majority of patients were able to be discharged home. However, the authors have also highlighted an increasing rate of ingestions over time. The most commonly ingested foreign bodies are coins, toys, jewelry, batteries, and magnets.[1] The majority of these ingested foreign bodies pass though the gastrointestinal tract spontaneously and uneventfully.[1,2] However, some of the ingestions may result in complications either by getting impacted in sphincters and curvatures or due to the deleterious nature of ingested foreign bodies (button batteries, multiple magnets, and sharp objects).[2,3] Among the few methodologic limitations are that the database was not inclusive of fatalities and captured only patients who presented to EDs and hence, children who remained at home and those who sought care at a primary care provider's office were not included. Recommendations for prevention of FBI include not leaving small objects where children have access, storing button batteries safely in childproof containers, and keeping particularly dangerous products off the market. Future research should consider how to best prevent FBI.

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