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: NONINFERIORITY TRIAL: A noninferiority trial compares a new treatment that offers a nontherapy-based advantage over the current effective treatment. The advantage may be less toxicity, decreased cost, ease of use, or other benefits. However, investigators of noninferiority studies are not interested in determining potential therapeutic superiority over the current treatment. The new treatment demonstrates its preferred use if it is, at least, not clinically worse than the current treatment. Study investigators must state at the outset of the study how much worse the new treatment could be and still be considered clinically effective (eg, 10% worse). If the study results demonstrate that the new treatment's 95% CI lower limit exceeds the predetermined efficacy cutoff, the new treatment is deemed noninferior. An example is highlighted in the piece by Ashkenazi on page 303 regarding the article by Freedman et al (*JAMA* 2016;315:1966-74). The investigators picked 7.5% worse as the cutoff for rehydration failure. In fact, the new treatment (dilute apple juice) was not only noninferior, it was actually superior to treatment with oral electrolyte solution.

LITERATURE SEARCH PEARL: HTA DATABASE CANADIAN REPOSITORY: Health technology assessment (HTA) is a process that systematically summarizes information on medical, economic, ethical, and social effects related to health technology. Introduced in 2015, the HTA Database Canadian Repository (www.crd.york.ac.uk/PanHTA) is a freely available electronic storehouse of Canadian, British, and international HTA reports. The United Kingdom's National Institute for Health Research sponsors the Database, and the University of York Centre for Reviews and Dissemination administers it. Many HTA Database reports (eg, economic health analyses, in-progress reports) are typically found only in the gray literature. The HTA Database links to the Database of Abstracts of Reviews of Effects, the Cochrane reviews, the National Health Service Economic Evaluation Database of assessed economic evaluations, and others. Depending on the specific source, some reports are critically appraised and others are not. Records in languages other than English are translated.

– Jordan Hupert, MD

Dilute apple juice superior to electrolyte solution in mild dehydration

Freedman SB, Willan AR, Boutis K, Schuh S. Effect of Dilute Apple Juice and Preferred Fluids vs Electrolyte Maintenance Solution on Treatment Failure Among Children With Mild Gastroenteritis: A Randomized Clinical Trial. *JAMA* 2016;315:1966-74.

Question Is dilute apple juice noninferior to electrolyte solution in treating gastroenteritis?

Design Randomized, single-blind noninferiority trial.

Setting Pediatric emergency department in Toronto, Canada.

Participants Children with minimal dehydration, aged 6-60 months, with gastroenteritis.

Intervention Half-strength apple juice followed by preferred fluid versus apple-flavored electrolyte maintenance solution.

Outcomes Treatment failure defined as any of: intravenous rehydration, hospitalization, subsequent unscheduled physician encounter, protracted symptoms, crossover, 3% or more weight loss, or significant dehydration at follow-up. Noninferiority margin: 7.5% difference.

Main Results Dilute apple juice followed by preferred fluid was superior to electrolyte maintenance solution, absolute risk reduction 8.3% (97.5% CI, 2.0%-∞), number needed to treat 12 (97.5% CI, 0-50).

Conclusions Treatment with dilute apple juice was superior to electrolyte solution.

Commentary Oral rehydration solutions (ORS), physiologically based on glucose-coupled sodium absorption (~1:1 glucose:sodium), is advocated by both US[1] and European[2] guidelines to prevent and treat dehydration. Due to their high carbohydrate and low sodium content, fruit juices and soft drinks are discouraged[1,2] because the carbohydrates are incompletely absorbed, leading to augmented diarrhea and sometimes to hyponatremia.[3] This well-conducted, comparative study demonstrated that dilute apple juice followed with preferred fluids was not only noninferior, but superior to electrolyte maintenance solution in children with mild gastroenteritis. The key significant difference was the need for IV rehydration. However, children included had a mean age of 28 months and presented with no (68%) or minimal (32%) evidence of dehydration. The beneficial effect was greater among children

older than 24 months of age, who are, based on my experience, more likely to refuse ORS. The evidence may be translated to patient care with caution and certain limitations. This approach can be considered in older children (>24 months of age) living in high-income locations with no or minimal dehydration. Apparently in these settings, as juice-fed children consume more fluid and calories with higher weight gain,[3] the increased fluid and energy intake outweighs the carbohydrate load of the feeding solution.

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E-cigarette use associated with tobacco smoking

Leventhal AM, Strong DR, Kirkpatrick MG, Unger JB, Sussman S, Riggs NR, et al. Association of Electronic Cigarette Use With Initiation of Combustible Tobacco Product Smoking in Early Adolescence. *JAMA* 2015;314:700-7.

Question Among young adolescents, what is the association of electronic cigarette (e-cigarette) use with subsequent tobacco smoking initiation?

Design Prospective cohort.

Setting Ten public high schools in Los Angeles, California.

Participants Ninth grade students.

Intervention Self-report survey, repeated at 6- and 12-month follow-up.

Outcomes Combustible tobacco initiation.

Main Results E-cigarette use was associated with subsequent combustible tobacco product initiation, OR, 2.73 (95% CI, 2.00-3.73, adjusted for sociodemographic, environmental, and intrapersonal risk factors for smoking).

Conclusions Among young adolescents, e-cigarette use was associated with subsequent combustible tobacco product initiation.

Commentary This longitudinal cohort study found that baseline e-cigarette use was associated with increased likelihood of combustible tobacco initiation. This study garnered widespread attention in the tobacco control community, as prior evidence largely used cross-sectional data that cannot establish causality or temporal patterns of use.[1] Despite the longitudinal design, the data do not establish causality and instead may reflect a general tendency for tobacco product users to try other tobacco products, instead of a unique tendency in e-cigarette users. A strength of this study is the persistence of the findings with adjustment for multiple confounders that have previously been shown to heighten risk of tobacco use. Additionally, it informs the public health debate regarding e-cigarettes, which weighs the potential benefits of smoking cessation in adults with the potential that e-cigarettes promote cigarette initiation and adverse health outcomes in adolescents. The study's findings have now been replicated,[2] and this growing evidence base highlights our duty to carefully consider the protection of youth when formulating e-cigarette policies and regulations.

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Adolescent BMI greater than 50% is associated with adult cardiovascular-death risk

Twig G, Yaniv G, Levine H, Leiba A, Goldberger N, Derazne E, et al. Body-Mass Index in 2.3 Million Adolescents and Cardiovascular Death in Adulthood. *N Engl J Med* 2016;374:2430-40.

Question What is the association of adult cardiovascular death (CVD) among obese adolescents, compared with adolescents who are not obese?

Design Retrospective, longitudinal data-set analysis.

Setting Israel.

Participants Jewish Israeli adolescents, 16-19 years old.

Intervention Body-mass index (BMI).

Outcomes CVD.

Main Results Multivariable analysis noted graded CVD risk among adolescents in the 50th to 74th percentiles of BMI (ie, within the accepted normal range). The obese group compared with those in the 5th to 24th percentiles demonstrated increased CVD risk: adjusted hazard ratio 4.9 (95% CI, 3.9-6.1) for coronary heart disease, 2.6 (95% CI, 1.7-4.1) for stroke, 2.1 (95% CI, 1.5-2.9) for sudden death, and 3.5 (95% CI, 2.9-4.1) for all-cause mortality.

Conclusions BMI grater than 50% was associated with increased CVD risk.

Commentary This large follow-up study of Israeli adolescents found that BMI is virtually log-linearly associated with CVD and only slight nonlinearity was found for all-cause mortality. This result is more striking because no information on body-composition was available, and even more so because underweight males may have a low level of muscle mass. Why are the results so different from results in middle-aged populations, suggesting that normal weight, or even slight overweight, could be associated with lower mortality?[1] The obvious reason is that in this young and healthy population there is no reverse causality. In a middle-age population, lean persons are a mixed group of healthy lean persons and persons suffering unintentional weight loss due to disease. This study clearly shows that there is no "obesity paradox": a healthy BMI is a low BMI, with the obvious exception of those having high muscle mass. Although it may be difficult to accept that many people in modern Western society suffer the health consequences of excess weight, the evidence from this study suggests just that.

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Viral PCR testing associated with decreased healthcare resource utilization

Subramony A, Zachariah P, Krones A, Whittier S, Saiman L. Impact of Multiplex Polymerase Chain Reaction Testing for Respiratory Pathogens on Healthcare Resource Utilization for Pediatric Inpatients. *J Pediatr* 2016;173:196-201.

Question What is the association of viral multiplex polymerase chain reaction (mPCR) testing with healthcare resource utilization?

Design Retrospective cohort study.

Setting New York-Presbyterian Morgan Stanley Children's Hospital.

Participants Hospitalized infants, children, and adolescents under 18 years of age.

Intervention mPCR testing for viruses or not.

Outcomes Use of antibiotics, chest radiographs, and isolation precautions.

Main Results Multivariable regression demonstrated mPCR testing decreased the likelihood of antibiotic use ≥2 days, OR, 0.5 (95% CI, 0.5-0.6), chest radiographs at admission, OR, 0.4 (95% CI, 0.3-0.4), and increased the likelihood of isolation for ≥2 days, OR, 2.4 (95% CI, 2.1-2.8) compared with the group without mPCR.

Conclusions mPCR use was significantly associated with decreased healthcare resource utilization and increased isolation precautions.

Commentary This study attempted to demonstrate that implementation of an mPCR assay resulted in clinical utilization changes observed pre- and postimplementation. It is crucial that such quasi-experimental studies identify and control for external confounders.[1] Although the authors provide reassurances, results could be confounded by an apparent increase in testing observed between the periods. Reassuring details of the study's validity include two winter viral seasons were monitored both pre- and postintervention and the prevalence of respiratory syncytial virus and influenza was similar. Antibiotic utilization did not differ pre- and postintervention in a control cohort with acute gastroenteritis. Finally, data here are similar to those of others.[2] Overall these data help justify mPCR costs. Importantly, results were available with ". . .a turnaround time of approximately 3 hours from order entry to results being viewed by providers." Delays in the turnaround of results, due to specific mPCR test characteristics or laboratory staffing, could attenuate this impact. Providers should cautiously interpret the results of mPCR respiratory assays as viral detection may be prolonged, particularly in young children and in patients with rhinovirus.[3] Important areas for future research include understanding the impact of these assays on neonates, infection control outcomes, timely administration of antivirals to patients with influenza, duration of hospitalization, and hospitalization costs.

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Early allergenic-food introduction does not reduce subsequent food allergy development

Perkin MR, Logan K, Tseng A, Raji B, Ayis S, Peacock J, et al. Randomized Trial of Introduction of Allergenic Foods in Breast-Fed Infants. *N Engl J Med* 2016;374:1733-43.

Question Does early allergenic-food introduction to infants reduce later allergy development?

Design Randomized, controlled trial.

Setting Single site in the United Kingdom.

Participants Exclusively breast-fed infants who were 3 months of age.

Intervention Six allergenic foods (peanut, cooked egg, cow's milk, sesame, whitefish, and wheat) introduced, one at a time, between 3-6 months of age versus no introduction.

Outcomes Food allergy to one or more of the six foods between 1-3 years of age.

Main Results Intention-to-treat analysis did not detect a difference in food-allergy development: absolute risk reduction 1.5% (95% CI, −1.3%-4.3%).

Conclusions Early allergenic-food introduction did not prevent subsequent food allergy.

Commentary The study by Perkin et al provides some insight as to what age allergenic-foods should be introduced to an infant's diet. Avoiding the early introduction of allergenic foods is feasible (97.4% in the control group did not consume any allergenic food before 5 months). Early, massive allergenic-food introduction is difficult (only 42.3% in the early-introduction group consumed at least 5 of the allergenic foods in adequate amounts between 3 and 6 months of age). Early introduction, based on per-protocol (not intention-to-treat) analysis may reduce the incidence of allergy to some foods (eggs and peanuts) but not to all. Despite some unavoidable methodologic limitations (selection, detection and attrition), the Enquiring about Tolerance (EAT), Perkin et al, trial seems to cool enthusiasm aroused by the Learning Early About Peanut allergy study that, on the model of peanut introduction, early introduction of any food may reduce the frequency of subsequent allergy to that particular food.[1] Additional studies, from different countries, climates, and culinary traditions, among infants in different risk categories may enhance the dataset from which we provide solid food introduction guidelines. These studies are much needed, as food allergy appears to be rising. The EAT trial noted a 5.4% hen-egg allergy prevalence in the control group, exceeding that reported (2.2%) in an epidemiologic UK study.[2]

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