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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3. Valois S, Costa-Ribeiro H Jr, Mattos A, Ribeiro TC, Mendes CM, Lifshitz F. Controlled, double-blind, randomized clinical trial to evaluate the impact of fruit juice consumption on the evolution of infants with acute diarrhea. Nutr J 2004;4:23-30.

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.