Current Best Evidence: Translating Best Evidence into Best Care

EDITOR’S NOTE: Studies for this issue were identified using alerts from Archives of Disease in Childhood-Education and Practice, Archives of Disease in Childhood-Fetal and Neonatal, Archives of Disease in Childhood, British Medical Journal, Journal of the American Medical Association, New England Journal of Medicine, Pediatric Infectious Disease Journal, Pediatrics, The Journal of Pediatrics, and The Lancet. Search terms were “paediatrics” [All Fields] OR “pediatrics” [All Fields] OR “pediatrics” [MeSH Terms]. In addition, studies also were identified using the Clinical Queries feature of PubMed. Cleo Pappas, MLIS, Library of the Health Sciences, University of Illinois at Chicago, contributed to the review and selection of this month’s abstracts.

—Jordan Hupert, MD

EBM PEARL: THE 5 RULES OF CAUSATION: As opposed to randomized controlled trials, nonrandomized studies assessing association between an exposure and an outcome are plentiful in the medical literature. However, given their higher chance for systematic bias, results demonstrating a statistically significant association do not prove causality. There are 5 rules that may suggest a causative link: (1) it is clear that the exposure preceded the outcome; (2) there is a dose-response effect; (3) demonstration of opposite outcomes from dechallenge-rechallenge exposures; (4) other studies demonstrate similar results; and (5) the association is biologically plausible. See the review of the study by Suglia et al (see piece by Shi on page 1241 regarding article Suglia et al, J Pediatr 2013;163:1323-8), for an illustration of rules 2 and 4.

—Jordan Hupert, MD

LIBRARIAN PEARL GOOGLE: Everyone resorts, at times, to searching with Google. There are aids available to minimize irrelevant hits, making your retrievals more specific. Quotation marks around your search terms tell Google to search for the words enclosed as if they were one word. The use of parentheses narrows your search further. The acronym NLM (National Library of Medicine) further narrows the search. Finally, adding the purpose of the search results in an even more precise search (although all Google searches are highly sensitive). For example, the search for liver cancer, retrieves 40 900 000 results; the search for “liver cancer” AND (prognosis OR “life expectancy” OR prospects OR prediction) AND (Chicago OR Minneapolis) AND NLM retrieves 330 000 results. Note that quotation marks may be used within parentheses and that stop words such as AND and OR are capitalized so the database recognizes them as part of the search command.

—Cleo Pappas, MLIS

Hypotonic IV fluid administration is associated with hyponatremia


Question Among hospitalized children receiving maintenance intravenous fluid (IVF), what is the association of hypotonic versus isotonic fluid administration with hyponatremia?

Design Chart review cohort.

Setting Lucile Packard Children’s Hospital.

Participants All hospitalized children between April 2009 and March 2011.

Intervention Hypotonic-versus isotonic IVF administration.

Outcomes Odds of developing hyponatremia.

Main Results Hyponatremia developed in 260 (38.6%) children who received hypotonic fluids and 104 (27.8%) of those who received isotonic fluids (unadjusted OR 1.63; 95% CI, 1.24-2.15). Multivariable analysis identified additional factors associated with the development of hyponatremia, including surgical admission (adjusted OR [aOR] 1.44, 95% CI, 1.09-1.91), cardiac admitting diagnosis (aOR 2.08, 95% CI, 1.34-3.20), and hematology/ oncology admitting diagnosis (aOR 2.37, 95% CI, 1.74-3.25).

Conclusions Administration of hypotonic maintenance fluids compared with isotonic fluids was associated with a greater risk of developing hospital-acquired hyponatremia.

Commentary Carandang et al confirm that the risk of hospital-acquired hyponatremia is not eliminated by, but rather reduced or delayed with isotonic maintenance IVF. It also suggests an evolution in IVF practice, at least in one center, since the beginning of this fierce debate over 10 years ago.1 Hypotonic fluids were used in 58% surgical and only 12% of neurologic/neurosurgical patients in this study, compared with a 92% rate reported in 2008.8 However, hypotonic IVF was still the fluid of choice, particularly in younger children and in the majority of medical conditions, despite consistent reports of excess antidiuretic hormone secretion in such patients.3 This
study provides the following key take home messages: (1) hypotonic IVF use in surgical, cardiac, and hematology/oncology patients is strongly predictive of hospital-acquired hyponatremia; (2) IVF therapy should therefore be decided by these patient risk factors, dictated by therapeutic goals, and accompanied by monitoring of those endpoints— is isotonic fluids are the undisputed fluids of choice if the goals are intravascular volume expansion or to reduce the risk of hyponatremia; and (3) hypotonic fluids may be appropriate if the goal is to correct a free water deficit or to reduce the solute load, as may be desired in cardiac patients.

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No association of HPV vaccination with serious adverse events


Question Among adolescent girls, what is the rate of adverse events in those who received, compared with those who did not receive, the quadrivalent human papillomavirus vaccine (qHPV)?

Design Register-based cohort study.

Setting Denmark and Sweden, October 2006, to December 2010.

Participants 997 585 girls aged 10-17 years.

Intervention qHPV.

Outcomes Incident hospital diagnosed autoimmune, neurologic, and venous thromboembolic events. For outcomes where the rate ratio was significantly increased, three criteria were regarded as signal strengthening: (1) analysis based on 20 or more vaccine exposed cases; (2) rate ratio 3.0 or more; and (3) significantly increased rate ratio in country specific analyses.

Main Results Exposure to qHPV was significantly associated with an increase only in Behcet syndrome, Raynaud disease, and type 1 diabetes. Each of these three outcomes fulfilled only one of three predefined signal strengthening criteria. Furthermore, the pattern of distribution in time after vaccination was random for all three.

Conclusions This study found no evidence supporting associations between exposure to qHPV and autoimmune, neurologic, and venous thromboembolic adverse events.

Commentary Despite the recommendation for universal qHPV of adolescent girls in 2007 (and males in 2011), qHPV rates remain substantially lower than other adolescent vaccines (meningococcal and tetanus, diphtheria, and pertussis vaccines) in the US.1 Concerns about vaccine safety by parents is a well-known barrier to vaccination in general, but such fear is often heightened for newer vaccines as parents question the extent to which a new vaccine has been tested.2 This study examines an important issue—the risk of serious adverse events after qHPV among adolescent girls. The setting of the study (Denmark and Sweden) allows for a more robust analysis than previous studies have been able to accomplish by using the national database in each country. The authors used rigorous methods to measure rates of qHPV vaccination and potential adverse events. As the authors note, data on the date of diagnosis of disease or onset of symptoms were not included in this study, but such information would improve our understanding of how many potential adverse events had symptoms prior to vaccination.

Though many ‘new’ medical interventions draw a healthy dose of skepticism by the public, vaccines suffer a disproportionately high burden of distrust. The study by Arnheim-Dalström et al is an important contribution to the growing literature about the safety of qHPV. However, because fear sits much deeper than logic in hearts of parents, we will undoubtedly have to continue to study the safety of this vaccine for years to come.

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References


Setting University of Rochester, New York.

Participants Patients with syncope referred to cardiology.

Intervention History and physical exam plus ECG compared with cardiology evaluation.

Outcomes Test characteristics of distinguishing features of cardiac-related syncope.

Main Results In patients with cardiac-related compared with vasovagal syncope, the presence of the following 4 previously identified predictors of cardiac etiology were assessed: (1) syncope surrounding activity, 65% vs 18% (P < .001); (2) family history of cardiac disease or sudden cardiac death, 41% vs 25% (P = .2); (3) physical examination supporting cardiac diagnosis, 29% vs 0% (P < .001); and (4) abnormal findings on ECG, 76% vs 0%, (P < .001) respectively. Any one of these four characteristics had a sensitivity of 100% (95% CI, 82% to 100%) and specificity of 60% (95% CI, 49% to 69%), +LR 2.5 (95% CI, 1.9 to 3.2) and –LR 0 (95% CI, 0 to 0.72).

Conclusions A screening tool that includes history, physical examination, and ECG, accurately identifies patients requiring further evaluation for a cardiac etiology.

Commentary Nevery 40% of people will experience one or more episodes of syncope during their lives, most by age 20 years with a mode of 15 years of age. Syncope—one form of transient loss of consciousness that also includes seizures, intoxication, conversion, and mild traumatic brain injury—is defined as transient global cerebral hypoperfusion characterized by rapid onset, short duration, and spontaneous complete recovery. It is classified into 3 groups: (1) reflex syncope—including the vasovagal type; (2) syncope due to orthostatic hypotension; and (3) cardiogenic syncope, uncommon in pediatrics but may have dire consequences. Tretter and Kavey identified characteristics distinguishing cardiogenic from reflex syncope: history, physical examination, and ECG. However, the strength of the study was diminished in four ways that may have affected the precision and/or numerical value of the sensitivity and specificity: (1) the infrequency of cardiogenic presentations included (eg, Wolff-Parkinson-White syndrome, a common cause of cardiogenic syncope was not represented); (2) use of billing codes to identify patients, excluding both patients with other forms of syncope and patients without syncope but in whom syncope was ruled out; (3) patients with aborted sudden cardiac death, a non-syncopal event, were included; and (4) history, physical examination, and ECG interpretation are operator dependent. Future studies should compare all patients with syncope presenting with the clinic or Emergency Department with evaluation by cardiology.

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References


Soda consumption is associated with negative behavior in young children


Question Among young children, what is the association of soda consumption with negative behavior?

Design Prospective birth cohort from the Fragile Families and Child Wellbeing Study.

Setting 20 large US cities.

Participants Children age 60 months.

Intervention Daily soda consumption vs. none.

Main Results In analyses adjusted for sociodemographic factors, consuming 1 (β, 0.7; 95% CI, 0.1-1.4), 2 (β, 1.8; 95% CI, 0.8-2.7), 3 (β, 2.0; 95% CI, 0.6-3.4), or 4 or more (β, 4.7; 95% CI, 3.2-6.2) servings was associated with a higher aggressive behavior score compared with consuming no soda.

Conclusions Soda consumption is associated with negative behavior among very young children.

Commentary During the past two decades, there have been substantial studies on the adverse effects of soft drinks on human health, especially chronic disease among adults. Findings from these studies have led to changes in policies (eg, taxing soft drinks) in some countries. The study by Suglia et al focuses on soft drinks and behavior among children. Consistent with findings among adolescents in Norway and US, high soft drink consumption is positively related to behavior problems in children age 5 years. The study is important because of its large sample size and ability to adjust for a range of confounding factors. The study’s findings are supported by existing evidence. In addition to the chemicals in soft drinks mentioned by the authors, phthalates from plastic packaging may also explain the link. A high maternal prenatal urinary phthalates level is associated with child behavior problems at age 3 years. Data from the National Health and Nutrition Examination Survey suggest that there is an association between phthalates and attention deficit disorder in children. High consumption of soft drinks among young children is of great concern and supports focusing attention towards reducing consumption.
**Flow resistant caps prevent the rapid ingestion of liquid medicine**

Lovegrove MC, Hon S, Geller RJ, Rose KO, Hampton LM, Bradley J, et al. Efficacy of flow resistant restrictors (FRs), compared with child-proof caps, in delaying ingestion of the medicine?

**Question** Among preschool children, what is the benefit of liquid medicine bottles with flow resistant restrictors (FRs), compared with child-proof caps, in delaying ingestion of the medicine?

**Design** Block randomized trial.

**Setting** 5 preschools in Atlanta, Georgia.

**Participants** Children 36-59 months. FRs or not.

**Outcomes** Proportions of children who emptied bottles, removed ≥25 mL (≥5 typical doses), and removed ≥5 mL (≥1 typical dose) of test liquid.

**Main Results** 96% (25 of 26) of the open control bottles and 82% (68 of 83) of the incompletely closed control bottles were emptied within 2 minutes. Only 6% (7 of 110) of the bottles with FRs were emptied during the 10-minute testing period, none before 6 minutes. NNT, open vs FR, 1.1 (95% CI, 1.0, 1.2); incompletely closed vs FR, 1.3 (95% CI 1.2, 1.5).

**Conclusions** Our findings suggest that adding FRs to liquid medicine bottles limits the accessibility of their contents to young children.

**Commentary** Each year, hundreds of thousands of US children under 5 years of age manage to grab a bottle of medication and drink it, generally because the cap was left off or not firmly put back into place. Although changes in labeling and safety warnings have reduced the overall number of certain pediatric overdoses, unsupervised ingestions have remained stable or even increased. Recently, innovations in packaging have emerged to prevent these overdoses. One such approach is flow restriction at the bottle opening, combined with a syringe for withdrawal and dosing. Lovegrove et al tested the impact of flow restriction by giving 3- and 4-year-old children the opportunity to handle different types of medication bottles. Although the majority of the children emptied standard bottles left open or inadequately closed, few were able to remove significant amounts from the bottles with flow restriction. This safety feature works, and expanding its use across a broad range of medications could dramatically reduce unintentional ingestions by young children.

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**References**


**Reference**


**Also noted**


In the November 2014 Current Best Evidence section, Fernandes presented a commentary of the study by Skjerven et al, which demonstrated superiority of on-demand vs. fixed-schedule nebulized inhalations in bronchiolitis, and that saline and racemic adrenaline (epinephrine) performed identically. A “translation” query was posed to one of the co-authors of the original article published in N Engl J Med, Håvard Ove Skjerven, MD.

According to Skjerven, Oslo University Hospital and Fredrikstad, together contributing more than 50% of the patients to the study, adjusted their management of bronchiolitis in accordance with the results of their study. In addition, Skjerven participated in revising the Norwegian national recommendations: “The Norwegian Pediatric Association publish[es] guidelines [on] acute and general pediatrics regularly. I was invited to contribute to the latest update on bronchiolitis, published in January, 2013. We took into account the results from the [randomized controlled trial] that we presented at the European Respiratory Society’s Congress in 2012 [basically similar to (our) article]. We [modified] the recommendation of use of inhaled adrenaline from up to every hour as standard on all patients hospitalized to:(1) contraindicated in children less than 3 months; (2) second choice after saline inhalations; (3) a trial may be tried, but only to be continued if [there is a] significant, objective effect; and (4) always prescribed as ‘on demand.’”

**Reference**