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: THE R(a)PID Approach: R(a)PID is a mnemonic and method for the "rapid" appraisal of therapy articles. It was developed a decade ago at the University of Illinois at Chicago. The objective of this method is to focus quickly on key elements of validity and results, affording a reasonable estimate of a study's quality and applicability. In a modern clinical study, much of the information required may be culled from the abstract. "R" is for randomized. Check the Abstract and/or the Methods section for randomization and look for blinding. These 2 validity issues are typically mentioned fairly close to each other. Then look at Table 1, which almost always is the list of the randomized groups' characteristics, to determine whether the randomization worked (no significant *P* values). "P" is for population and primary outcome. Both pieces of information can often be found in the Abstract. If not, check the beginning part of the Methods section for the population and the latter part of the Methods section just prior to the Statistics section for the outcomes. Identify who got into the study (are they similar to your patients?) and what were the measured outcomes (are the outcomes of clinical interest to you?). "I" is for intention to treat. The quickest way to determine this is to find Figure 1, which is typically the participation flow diagram. Compare the number of people randomized in each group (often the boxes of the diagram near the top) to the number of people analyzed (typically the bottom boxes of the diagram). These numbers should be identical (ideally). If not, there should be a clear explanation of what happened, and the number missing should be a small percentage of the group's total. Also, look in the Methods section for an explicit mention of intention to treat. Finally, "D" is for decision. In most instances you will be looking for outcomes that include percent of people or number of people who experienced the outcome. Look for absolute risk reduction and number needed to treat, both with their 95% confidence intervals, to identify statistical significance.

CRITICAL STATISTICAL DISTINCTION PEARL: TYPE 1 AND TYPE 2 ERRORS: To understand Type 1 and 2 errors we need first to discuss the null hypothesis. The null hypothesis asserts, for example, that a new treatment given to 1 of 2 similar populations will have no effect. A researcher performs an experiment and finds that the group that received the new treatment improved more than the group that did not receive the new treatment. If the improvement is due to sampling or experimental error, the null hypothesis is sustained. If not, the null hypothesis is rejected. How this is determined is based on how much difference between groups is considered "sampling or experimental error." The numeric description of this is called the *P* value, the probability the results observed are consistent with the null hypothesis. By convention, a $P \geq 5\%$ means the groups are statistically identical with respect to results of the new treatment, and the null hypothesis is sustained. A $P < 5\%$ means that the groups are different with respect to the new treatment, and the null hypothesis is rejected. A Type 1 error occurs if we reject the null hypothesis but in fact there is no difference between the groups (ie, the null hypothesis is correct). A Type 2 error occurs if we accept the null hypothesis but in fact there is a difference between the groups. The Type 1 error is a false positive and the Type 2 error is a false negative. The probability of avoiding a Type 2 error is the power. By usual convention, power ≥80% is considered adequate to accept the null hypothesis. Reducing one error type typically increases the other type. Both Type 1 and Type 2 errors are reduced with an increase in the number of study patients. However, error is never reduced to zero.

—Jordan Hupert, MD

AAP recommends isotonic maintenance intravenous fluid

Feld LG, Neuspiel DR, Foster BA, Leu MG, Garber MD, Austin K, et al. Clinical Practice Guideline: Maintenance Intravenous Fluids in Children. *Pediatrics* 2018;142.pii: e20183083.

Question Among children receiving maintenance intravenous fluid (IVF), what is the association of hypotonic sodium IVF, compared with isotonic sodium solutions, in developing hyponatremia?

Design Systematic review and clinical practice guideline.

Setting Multi-national.

Participants Inpatient children, 28 days – 18 years, receiving maintenance IVF.

Intervention Hypo- versus isotonic maintenance IVF.

Outcomes Serum sodium.

Conclusions "The American Academy of Pediatrics recommends that patients 28 days to 18 years of age requiring maintenance IVFs should receive isotonic solutions with appropriate potassium chloride and dextrose because they significantly decrease the risk of developing hyponatremia (evidence quality: A; recommendation strength: strong)."

Commentary The AAP Subcommittee on Fluid and Electrolyte Therapy provides a review of published data relative to the topic and a rational, though unfortunately incomplete evidence-based approach to maintenance fluid therapy. As highlighted, the provision of isotonic IVF to pediatric inpatients lessens the risk of iatrogenic electrolyte abnormalities. However, optimal delivery of fluid and electrolytes requires providers to understand that daily "maintenance" water and electrolytes needs vary among individuals, are impacted by disease states, and change as patient conditions evolve. The Guideline discusses tonicity of parenteral fluids with little mention of volume infused relative to true water needs. Estimated maintenance water requirements, as published by Holliday and Segar,[1] are based on children without significant medical or surgical complications, a population very different than that encountered in contemporary practice involving conditions often associated with increased serum vasopressin (AVP) levels. It is not surprising that hyponatremia has commonly been seen in children provided hypotonic fluid, as elevated AVP levels limit renal water losses to far less than estimated by Holliday and Segar for their calculations. Prudent efforts to understand and limit water intake to an individual's "maintenance needs" (insensible plus urinary losses), may additionally lessen the risk of hyponatremia. There remains a need to expand the recent Guidelines to include discussion of volumes of fluid to be administered.

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AR101 prevents peanut allergy reactions in highly peanut-allergic children

Vickery BP, Vereda A, Casale TB, Beyer K, du Toit G, Hourihane JO, et al. AR101 Oral Immunotherapy for Peanut Allergy. *N Engl J Med* 2018;379:1991-2001.

Question Among highly peanut-allergic children, what is the therapeutic efficacy of AR101 (a peanut-derived, oral biologic drug), compared with placebo, in preventing an allergic reaction to subsequently ingested peanut?

Design Randomized, controlled trial.

Setting 66 sites in 10 countries in North America and Europe.

Participants Children 4-17 years of age, highly allergic to peanut.

Intervention AR101 versus placebo in a 3:1 randomization pattern: 372 and 124 patients, respectively.

Outcomes The proportion of patients who could ingest a peanut challenge dose of 600 mg or more, without dose-limiting symptoms.

Main Results 600 mg or more of peanut was tolerated more by those treated with AR101 than those receiving placebo: 250 of 372 and 5 of 124 patients in the AR101 and placebo groups, respectively, absolute risk reduction 63.2% (95% CI, 57.3% - 69.1%), number needed to treat 1.6 (95% CI, 1.4 – 1.7).

Conclusions AR101 treatment resulted in a sizable peanut allergic-reaction reduction among highly peanut-allergic children.

Commentary Peanut allergy is a global problem. Millions of patients are continuously under the threat of accidental exposure (a significant cause of anaphylaxis and quality of life impairment). The current standard of care, unsatisfactory for all stakeholders, is based upon avoidance of and treatment for accidental exposure. Food immunotherapy represents the most promising option on the horizon despite some issues that will require elucidation (eg, safety and long-term efficacy).[1] Vickery et al provide robust evidence for the efficacy of AR101 in a study that included almost 500 children. Their results are expected to have a meaningful and tangible impact on the expected real-life risk of peanut-allergic patients. A single 300 mg peanut protein dose (secondary outcome) did not induce significant symptoms. Tolerance to 300 mg peanut protein among patients who previously reacted to 100 mg or less, reduces the risk of an accidental reaction by more than 95%.[2] Although unanswered questions remain on widespread applicability, different populations/treatment schemes, and longer duration, Vickery et al set up a clear milestone along the path toward the approval of peanut allergy treatments.

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P.RdR. was involved in the AR101 study and served as a speaker for Aimmune, the company that developed AR101.

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2. Baumert JL, Taylor SL, Koppelman SJ. Quantitative assessment of the safety benefits associated with increasing clinical peanut thresholds through immunotherapy. J Allergy Clin Immunol Pract 2018;6:457-65.e4.

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Afebrile infants presenting to the emergency department with only a history of fever have a significant risk of serious bacterial infection

Ramgopal S, Janofsky S, Zuckerbraun NS, Ramilo O, Mahajan P, Kuppermann N, et al. Risk of Serious Bacterial Infection in Infants Aged ≤60 Days Presenting to Emergency Departments with a History of Fever Only. *J Pediatr* 2019;204:191-5.

Question Among infants with only a history of fever but present afebrile to the emergency department (ED), what is the association with serious bacterial infection (SBI), compared with infants who present with ED-documented fever?

Design Secondary analysis of a multicenter prospective cohort study.

Setting 26 geographically diverse EDs in the Pediatric Emergency Care Applied Research Network.

Participants Infants ≤60 days with fever (defined as a temperature ≥38°C).

Intervention History of fever versus documented fever in the ED.

Outcomes Serious bacterial infection (urinary tract infection [UTI], bacteremia, and/or bacterial meningitis).

Main Results Of 1233 (32.2%) infants who were afebrile in the ED, 108 (8.8%) had SBI, compared with 2592 infants (67.8%) who were febrile in the ED, 331 (12.8%) of whom had SBI (in both groups most with UTI), RR 0.68 (95% CI, 0.56-0.84).

Conclusions Risk of SBI in infants presenting afebrile to the ED with only a history of fever was 2/3 the risk of infants with fever in the ED. Nevertheless, this represents a not-insignificant risk.

Commentary There is a great variability in the management of the young febrile infant.[1] 25-30% of young infants with a history of fever are afebrile on arrival to the ED.[2] Uncertainty over the prevalence of SBI in infants presenting afebrile to the ED may contribute to management variability. In the study conducted by Ramgopal et al, the prevalence of SBI was lower among infants afebrile on ED presentation compared with those who were febrile. Nevertheless, the rate of SBI remained substantial and the rate of invasive bacterial infection (bacteremia and meningitis) did not show significant differences among the infants who did and did not have fever documented in the ED. This suggests that clinical and laboratory evaluation in the ED should not be altered based solely on the infant's temperature at ED presentation.

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Primary-care-based child maltreatment interventions have not demonstrated efficacy

Viswanathan M, Fraser JG, Pan H, Morgenlander M, McKeeman JL, Forman-Hoffman VL, et al. Primary Care Interventions to Prevent Child Maltreatment: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA* 2018;320:2129-40.

Question Among children without a history of maltreatment, what is the efficacy of primary-care-based interventions, compared with no intervention, in preventing child maltreatment?

Design Systematic review.

Setting 49 countries categorized as very highly developed by the 2015 Human Development Index.

Participants Children without known exposure or signs/symptoms of child maltreatment.

Intervention Primary-care-based interventions

Outcomes At least one direct maltreatment measure (linked to caregiver) or proxy maltreatment measure (eg, removal from home).

Main Results The 22 studies included in the systematic review yielded no significant results or yielded inconsistent results for primary-care-linked child maltreatment prevention.

Conclusions Primary-care-based interventions did not prevent child maltreatment.

Commentary Recent estimates show that child maltreatment affects approximately 650 000-700 000 children in the US each year.[1] The long-term consequences of child maltreatment include numerous negative effects on future physical and mental health.[2] The effect of child maltreatment prevention programs, especially home visiting programs, remains uncertain. This systematic review of primary care interventions to prevent child maltreatment by Viswanathan et al included 22 RCTs spanning more than 3 decades. Though the findings did not show a statistically significant benefit after intervention, the authors described the complexity in studying these interventions and outcomes. Twenty-one of the 22 RCTs included home visiting programs, but they differed substantially in almost every aspect of study design,

likely contributing to the difficulty in assessment. Further investigation is needed to better understand ways to prevent child maltreatment. Perhaps future research should focus on specific interventions, such as interventions on risk factors for child maltreatment, which may in turn reduce or eliminate exposure to abuse and neglect as a secondary outcome.

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Lactobacillus administration does not affect acute gastroenteritis

Schnadower D, Tarr PI, Casper TC, Gorelick MH, Dean JM, O'Connell KJ, et al. Lactobacillus rhamnosus GG versus Placebo for Acute Gastroenteritis in Children. *N Engl J Med* 2018;379:2002-14.

Question Among children with acute gastroenteritis presenting to the emergency department (ED), what is the therapeutic efficacy of lactobacillus, compared with placebo, in ameliorating acute gastroenteritis?

Design Randomized, controlled trial.

Setting 10 pediatric EDs across the US.

Participants Children 3 months to 4 years of age with acute gastroenteritis (3 or more watery stools <7 days duration).

Intervention 5-day course of Lactobacillus rhamnosus versus placebo.

Outcomes Primary outcome: moderate-to-severe gastroenteritis, defined as an illness episode with a total score on the modified Vesikari scale of 9 or higher within 14 days after enrollment.

Main Results The Vesikari scale score of ≥9 was not different in the 2 groups: absolute risk reduction 0.88% (95% CI, -3.30%, 5.06%). Duration of diarrhea, vomiting, day-care absenteeism, and the rate of household transmission also did not differ between the 2 groups.

Conclusions Lactobacillus did not alter the course or severity of acute gastroenteritis in preschool children.

Commentary The lack of efficacy in the Schnadower et al study conflicts with several trials showing a reduction of diarrhea severity and duration in different settings. The use of a modified Vesikari score, onset of therapy, rotavirus immunization, and previous antibiotic courses, differ among trials. The Schnadower et al study sample size and subgroup analysis resolve most reproducibility issues. Also, it is unlikely that the North American microbiome, gastroenteritis etiology, or medical approach differ significantly from other developed parts of the world. In the same issue of the *NEJM*, another published negative RCT, with the same design and some authors in common, used a probiotic combination for which comparative data are not available.[1] Studies like these mark a novel trend in evidence-based medicine. Large, rigorous, RCTs challenge meta-analyses and dozens of heterogeneous studies of various quality that have previously provided the basis for acute gastroenteritis guidelines. Current guidelines recommend Lactobacillus GG as an adjunct to oral rehydration.[2] If the "no treat" option is applied widely, millions of children will be left without an active therapy while their parents request an effective intervention.[3]

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