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*, *The New England Journal of Medicine*, AAP daily briefing, and from customized EvidenceAlerts.

EBM PEARL: BONFERRONI CORRECTION: The Bonferroni correction is named for Carlo Bonferroni (1892-1960), an Italian statistician. The Bonferroni correction, as commonly employed, adjusts the probability of statistical significance, the *P* value, to account for multiple comparisons in a study. Multiple comparisons alone increase the likelihood of one comparison achieving statistical significance and increase the chance of a Type I error: concluding a significant effect is present when it is not. As an example, if $P = .05$ for a single comparison test in a study where the null hypothesis is true (there really is no difference between the two comparators), a significant result will be seen 1 out of 20 studies. If one performs 20 comparison tests in one study and the null hypothesis is true for each of 20 tests, the chance one of the tests will be positive is 0.64, not 0.05. The Bonferroni correction was designed to fix this problem. A mathematical approximation of the Bonferroni correction = (*P* value)/(number of comparison tests). There are some potential problems with the Bonferroni correction: in many situations, it is far too conservative. Also, as one decreases the Type 1 error, the chance of a Type II error (concluding a significant effect is not present when it is) increases. For an example of how the Bonferroni correction is used, see the article by Dhingra et al below.

CRITICAL STATISTICAL DISTINCTION PEARL: NON-INFERIORITY LIMITS OF EQUIVALENCE: Well-constructed non-inferiority studies define the relevant limits of clinical equivalence, with exact equivalence being 0 for result differences expressed in a linear fashion (x-y), and 1 for results expressed as a proportion (x/y). Dhingra et al, below, investigated the question of whether lower-dose zinc (which may cause less vomiting) compared with standard-dose zinc is clinically equivalent in treating acute diarrhea. The difference between the number of children with diarrheal stools after 5 days treated with standard-dose and lower-dose zinc was 1.2%. Dhingra et al defined, a priori, clinical equivalence as anything less than a 4% difference. 1.2% certainly fits that criterion. However, the critical statistical distinction learning point is that the answer lies in the confidence interval. The upper limit of the confidence interval was 3.3%, also less than the defined confidence interval, and demonstrating lower-dose zinc is clinically equivalent (non-inferior) to standard-dose zinc.

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Lower-dose zinc non-inferior to standard dose in diarrhea treatment and with less emesis

Dhingra U, Kisenge R, Sudfeld CR, Dhingra P, Somji S, Dutta A, et al. Lower-Dose Zinc for Childhood Diarrhea - A Randomized, Multicenter Trial. N Engl J Med 2020;383:1231-41.

Question Among children with diarrhea, what is the clinical efficacy of lower-dose zinc, compared to standard-dose zinc, in decreasing diarrhea and emesis – the latter associated with standard-dose zinc?

Design Non-inferior, randomized, controlled, double-blind study.

Setting India and Tanzania.

Participants 4500 children with acute diarrhea.

Intervention 5, 10, or 20 mg zinc sulfate daily for 14 days.

Outcomes Diarrhea duration more than 5 days, number of stools, and vomiting within 30 minutes of zinc administration. Non-inferiority: Upper limit of confidence interval within 4 percentage points of equivalence.

Main Results Children with diarrhea >5 days: 6.5%, 7.7%, and 7.2% in the 20, 10, and 5 mg groups, respectively: all comparisons with 20 mg <4% upper limit of the 98.75% CIs (instead of 95% CI, based on post hoc Bonferroni correction for multiple comparisons). Stool number demonstrated similar results. 19.3%, 15.6%, and 13.7% children vomited within 30 minutes of administration in the 20, 10, and 5 mg groups, respectively, with 10 and 5 mg doses superior to 20 mg. Number needed to treat, 27 (98.75% CI, 14 – 356) and 18 (98.75% CI, 11 – 48), for 10 mg and 5 mg compared with 20 mg, respectively.

Conclusions Lower-dose zinc demonstrated non-inferior diarrhea-duration-improvement and stool-number efficacy, and superior emesis control.

Commentary Therapeutic zinc (20 mg/d for 10-14 days) is currently recommended by the World Health Organization for treatment of acute diarrhea. This strategy has been shown

by several systematic reviews to reduce the duration of diarrhea. Unfortunately, vomiting, and in some cases nausea, is a known side effect which threatens acceptability. The evidence from this study is consistent with evidence from previous studies which reported a 14-50% elevated risk of vomiting following the first therapeutic zinc dose.[1] It is believed that zinc-induced vomiting is transient, has early onset (occurring within 10-30 minutes of treatment initiation) and indicative of a centrally-coordinated, clinically-insignificant neurological reflex to a novel, metallic taste. To improve acceptability, zinc supplementation must be coupled with community-level education regarding this seemingly benign side effect. Dhingra et al also reported that the lower zinc doses (5mg/d and 10mg/d) were non-inferior to the standard 20 mg/d dose with respect to efficacy on diarrhea. This finding, however, must be interpreted cautiously. As childhood diarrheal episodes generally last 2-3 days, treatment of prevalent cases (as was done in this study), significantly reduces the potential to detect an impact.

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Early cow's milk formula prevents milk protein allergy

Sakihara T, Otsuji K, Arakaki Y, Hamada K, Sugiura S, Ito K. Randomized trial of early infant formula introduction to prevent cow's milk allergy. J Allergy Clin Immunol 2020:S0091-6749(20)31225-2.

Question What is the therapeutic efficacy of cow's milk formula (CMF) compared with none, in preventing cow's milk allergy (CMA) among 1-2 month-old babies?

Design Randomized, controlled trial (RCT).

Setting 4 hospitals in Okinawa, Japan.

Participants Babies, at least 2000g, 35 weeks and <6 days old.

Intervention ≥10 mL of CMF daily versus none (breast milk +/- soy milk supplement as needed) starting between 1 and 2 months of age.

Outcomes CMA.

Main Results The absolute risk reduction was 6.0% (95% CI, 2.7% - 9.3%), number needed to treat, 17 (95% CI, 11 - 38), in favor of CMF ingestion.

Conclusions Daily CMF ingestion at 1-2 months of age prevents CMA.

Commentary To prevent food allergy, prolonged exclusive breastfeeding has been recommended. However, this preventive strategy has recently been questioned. Sakihara et al conducted an RCT demonstrating that daily ingestion of CMF at 1–2 months of age remarkably reduced CMA development. Prior to randomization, this study did not control feeding patterns, either to avoid or include CMF in the maternity hospital. We reported results from an RCT that CMA prevalence was reduced to 10% by avoiding CMF for the first 3 days of life.[1] Sakihara et al confirmed that none of the 31 participants who avoided CMF for the first 3 days of life developed CMA. Thus, results from these two RCTs are consistent and suggest that timing is critical: newborns should probably avoid consuming CMF for the first 3 days of life and start supplementing breastfeeding with CMF at the latest by 1 month of age.

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Early term-infant discharge associated with higher re-admission rates

Jones E, Taylor B, MacArthur C, Bradshaw S, Hope L, Cummins C. Early Postnatal Discharge for Infants: A Meta-analysis. Pediatrics 2020;146:e20193365.

Question Among full-term neonates, what is the impact of early discharge on medical-services utilization?

Design Systematic review and meta-analysis of randomized, controlled trials (RCT) and interrupted time-series (ITS) studies.

Setting International.

Participants Term neonates.

Intervention Early versus standard discharge.

Outcomes Increased use of medical services.

Main Results 15 studies met inclusion criteria. RCT meta-analysis demonstrated that infants discharged after both vaginal (48 hours post-partum) and cesarean (96 hours post-partum) births were more likely to be readmitted (within 28 days) compared to standard discharge: risk ratio, 1.70 (95% CI, 1.34 – 2.15). ITS study meta-analysis demonstrated a decreased proportion of infants re-admitted after

minimum postnatal-stay policies and legislation were introduced.

Conclusions Early discharge is associated with higher readmission rates; minimum stay policies and legislation suggest a long-term ameliorating effect.

Commentary Jones et al identified 15 out of 9,298 studies potentially related to the impact of short postpartum discharge for term infants. Although the findings of this study set a framework of evidence-based care, one may question in this era of personalized medicine, whether a one (or two) size approach "fits all" is optimal. In this regard, an individual study performed in a context similar to a clinician's own healthcare system, could provide relevant results in addition to the overall results of the meta-analysis. One would also expect that individual factors, such as gestational age week, multiple gestation, parity, and post-discharge access to care issues, all modify the risk profile of childbirth hospitalization and the risk of readmission. Ultimately, the clinician will weigh the evidence from this comprehensive meta-analysis in addition to consensus guidelines, such as from the American Academy of Pediatrics,[1] in implementing policies and directing individual patient care to optimize outcomes.

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Pediatric hypertension over a 6-year period

Kaelber DC, Localio AR, Ross M, Leon JB, Pace WD, Wasserman RC, Grundmeier RW, Steffes J, Fiks AG. Persistent Hypertension in Children and Adolescents: A 6-Year Cohort Study. Pediatrics 2020;146:e20193778.

Question Among children presenting for routine primary care, what is the natural history of those diagnosed with hypertension?

Design Retrospective cohort study utilizing the American Academy of Pediatrics Comparative Effectiveness Research through Collaborative Electronic Reporting Consortium data.

Setting 165 pediatric primary care sites among 30 health care systems.

Participants Children, 3 – 18 years old.

Intervention Blood pressure measurements over 2 consecutive 36-month periods.

Outcomes Hypertension rates (≥3 visits in which either the diastolic blood pressure and/or the systolic blood pressure was ≥95th percentile for age, height, and sex).

Main Results Of 398,079 patients, 89,347 and 43,825 had ≥3 blood pressure levels recorded in one and two consecutive 36-month periods respectively. 4.3% (95% CI, 4.1% - 4.5%) and 1.2% (95% CI, 1.1% - 1.3%) of the 43,825 met criteria for hypertension in the first 36-month period and both 36-month periods, respectively, and 2.1% (95% CI, 2.0% – 2.3%) had no abnormal blood pressures in the second 36-month period.

Conclusions Most children did not have a yearly blood pressure recorded. Almost half the children meeting diagnostic criteria for hypertension in the first 36-month period did not have any abnormal blood pressures in the second 36-month period.

Commentary This study demonstrates several important clinically relevant outcomes. First, in a large pediatric study population followed for 2 consecutive 36-month periods, only fewer than one-third of children had a yearly blood pressure measurement performed (guidelines recommend yearly blood pressure measurements). Second, among all subjects correctly diagnosed with abnormal blood-pressure values (hypertension or elevated blood pressure) in the first 36-month period, only half underwent adequate follow-up in the second 36-month period. Third, the diagnosis was confirmed in only less than one-half of children with abnormal blood pressure values. In particular, the percentage of subjects with a confirmed diagnosis of arterial hypertension was 1.8% in children correctly followed up over both 36-month periods. In our opinion, this prevalence of hypertension is not negligible, as there are very few chronic pathologic conditions that demonstrate such a high prevalence in the pediatric age group. Further, hypertension may have been underdiagnosed. This study employed highly restrictive hypertension diagnostic criteria: six consecutive elevated blood pressure measurements over 2 consecutive 36-months periods. If the child did not have ≥3 elevated blood pressures also in the second 36-month period, he was not considered to have hypertension. We feel that subjects diagnosed with an abnormal blood pressure in the first 36-month period, but not confirmed in the subsequent period, should still be followed up over time, as it is possible that they are at greater cardiovascular risk than children who always had normal blood pressure values.[1] Finally, the authors report that the prevalence of hypertension or of elevated blood pressure evaluated using the nomograms of the 2004 pediatric hypertension clinical practice guidelines (currently recommended by the European Society of Hypertension) was about half of that estimated by using the latest US guidelines, even if the normalization rates over time were similar. These findings leave open the question of which nomograms are most appropriate for defining hypertension in children.[2]

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Arrhythmias associated with SSRI use in children and young adults

Czaja AS, Anderson HD, Ghosh D, Davidson J, Campbell JD, Valuck RJ. Increased Odds of Ventricular Arrhythmias Associated with Selective Serotonin Reuptake Inhibitor Use among the Pediatric and Young Adult Population: A Case-Control Study. J Pediatr 2020;226:173-8.

Question Among children and young adults, what is the ventricular arrhythmia risk associated with selective serotonin reuptake inhibitor (SSRI) use?

Design Case–control study using the IQVIA PharMetrics Health Plan Claims Database from 2007 to 2018.

Setting 75 US-based managed care plans.

Participants Cases: at least one event between ages 2 and 24 years. Controls: 10-times cases matched with no events.

Intervention SSRI or none.

Outcomes Ventricular arrhythmia.

Main Results Adjusting for mental health and chronic conditions, SSRI use was associated with ventricular arrhythmia, OR 5.1 (95% CI, 1.2 - 21.4). Subgroup analysis of pediatric (2 - 17 years) versus young adult (18 – 24 years) SSRI use did not demonstrate a difference.

Conclusions Ventricular arrhythmia is associated with pediatric and young adult SSRI use.

Commentary Given the upward trend of antidepressant use in children and adolescents,[1] it is important to evaluate the cardiac risk associated with SSRI use. QT prolongation could be one of the most difficult adverse drug effects to be studied due to its rarity. Employing a large administrative claims database, Czaja et al demonstrated current SSRI exposure was associated with an elevated risk of ventricular arrhythmia. While the adjusted odds ratios (including specific SSRIs) were all considerably greater than one, most of them did not attain statistical significance. This again highlights the challenge of assessing such a rare event even with a large database. One potential limitation of this study is confounding by indication. As the study did not nest in patients with depression or receiving antidepressants, most controls were individuals without mental health conditions. This makes it difficult to separate the effect of SSRIs from the underlying conditions. The risk of associated QT prolongation and ventricular arrhythmia differs by age. The conclusion should be applied carefully for such a wide-ranging group, especially for a young population. Finally, as pediatric cases of torsade de pointes (an occasional prolonged-QT-syndrome complication) have been associated with other drug classes (eg, antifungals), one may consider alternatives to SSRIs associated with prolonged QT, if clinically appropriate.

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