

Translating Best Evidence into Best Care

EDITOR'S NOTE: Studies for this issue were identified using the Clinical Queries feature of PubMed, “hand” searching *JAMA Pediatrics*, *Pediatrics*, and *The Journal of Pediatrics*, and from customized EvidenceUpdates alerts.

EBM PEARL: STANDARD MEAN DIFFERENCE (SMD): The SMD is commonly used in meta-analysis to express a summary statistic when studies report results in terms of a continuous measurement, and when all included studies measure the same outcome but do so using different measures. The SMD is defined as the difference in means of two study groups, divided by the pooled standard deviation (SD) of the outcome (study variability). Therefore, two studies where the mean differences relative to the study outcome SDs are the same have the same SMD. Although the SMD is a useful statistical tool, its primary clinical use is to note whether the SMD is statistically significant and its magnitude. The higher the SMD magnitude, the higher the new treatment probability of benefit. An example of SMD use is in the piece by Devillier on page 1169 regarding the systematic review/meta-analysis by Di Bona et al; *JAMA Intern Med* 2015;175:1301-1309.

LITERATURE SEARCH PEARL: TRIP DATABASE: The Trip database (tripdatabase.com) is a medical literature search engine, developed in 1997, dedicated to providing high quality evidence. Trip originally stood for Turning Research Into Practice, but the developers no longer refer to this Trip acronym. Trip's unique feature is organizing retrieved literature by primary evidence sources (individual, primary research studies), secondary evidence sources (guidelines, synopses, systematic reviews), and ongoing research protocols. There are a number of other features, including a direct link to PubMed Clinical Queries, with a search result summary listed in Trip (generated from a high-specificity, “narrow” Clinical Queries search) and with the articles listed—via hyperlink—in PubMed (ncbi.nlm.nih.gov/pubmed). Trip “basic” is free; the premium version is available by subscription and includes simultaneous image and video searches and other expanded services.

—Jordan Hupert, MD

Allergic rhinitis treatment with sublingual immunotherapy

Di Bona D, Plaia A, Leto-Barone MS, La Piana S, Di Lorenzo G. Efficacy of Grass Pollen Allergen Sublingual Immunotherapy Tablets for Seasonal Allergic Rhinoconjunctivitis: A Systematic Review and Meta-analysis. *JAMA Intern Med*. 2015;175:1301-1309.

Question Among children with allergic rhinitis, what is the therapeutic efficacy of sublingual immunotherapy, compared with placebo, in ameliorating symptoms?

Design Meta-analysis of randomized controlled trials.

Setting US, Canada, Europe.

Participants Children and adults, 4 – 65 years old.

Intervention Grass-pollen-allergen sublingual immunotherapy tablets (SLIT) or placebo.

Outcomes Symptom score and medication score.

Main Results The symptom score (standard mean difference [SMD], -0.28 ; 95% CI, -0.37 to -0.19 ; $P < .001$) and the medication score (SMD, -0.24 ; 95% CI, -0.31 to -0.17 ; $P < .001$) demonstrated small treatment benefits.

Conclusions The meta-analysis demonstrated a small benefit of SLIT in reducing symptoms and in decreasing the use of symptomatic medication.

Commentary Di Bona et al suggest that the clinical benefit of SLIT is smaller than that of subcutaneous immunotherapy

(SCIT) or pharmacotherapy in grass-pollen-induced allergic rhinoconjunctivitis. Although the methodology of their meta-analysis was rigorous, their interpretation of the results is questionable. An effect size based on the standardized mean difference (the number of standard deviations between means), or Hedges g , is not a same as the “intervention effect” or “effect estimate” classically used in medicine. The relative clinical impact (RCI—the active vs. placebo difference between post-treatment symptom scores, as defined by the World Allergy Organization) appears to be more appropriate. In another study, the mean RCI was -29.6% for a five-grass pollen SLIT tablet, -19.2% for a timothy pollen SLIT tablet, -23.5% for nasal corticosteroids, -15.0% for H1-antihistamines, and -6.5% for montelukast.¹ Although our value of Hedges g for SLIT was similar to that reported by Di Bona et al, the RCI data suggest that grass pollen SLIT tablets had a greater clinical impact than second-generation antihistamines and montelukast and much the same mean clinical impact as nasal corticosteroids. These results are in line with the RCI-based study by Matricardi et al, which found that SCIT is at least as potent as pharmacotherapy in controlling the symptoms of seasonal allergic rhinitis.² Accordingly, the conclusions by Di Bona et al may be clinically misleading as they understate the benefit of SLIT tablets.

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Minority of college rapes committed by serial rapists

Swartout KM, Koss MP, White JW, Thompson MP, Abbey A, Bellis AL. Trajectory Analysis of the Campus Serial Rapist Assumption. *JAMA Pediatr* (2015). doi:10.1001/jamapediatrics.2015.0707.

Question Among college men who perpetrate rape, what is the relative group size of serial rapists?

Design Latent class growth analysis of two longitudinal data sets of sexual violence on college campuses.

Setting Two universities in the Southeastern US.

Participants College freshman.

Intervention The Sexual Experiences Survey.

Outcomes Rape perpetration.

Main Results 177 of 1645 participants (10.8%, 95% CI, 9.3% to 12.4%) reported having perpetrated at least one rape from 14 years of age through the end of college. 127 (7.7%, 95% CI, 6.5% to 9.1%) committed rape during college. Derivation and validation data sets were constructed. Within the validation data set, 25% (95% CI, 17% to 35%) of men who committed college rape, perpetrated rape across multiple academic years.

Conclusions A small group of men perpetrated rape across multiple college years (serial rapists); they constituted a significant minority of those who committed college rape.

Commentary Violence prevention requires that we understand what we are trying to prevent. This important research confirms that sexual aggressors are heterogeneous, with trajectories of persistent, initiating, and desisting perpetration.¹⁻³ There are numerous methodological challenges to understanding who commits assaults and how many. Understanding when assaults occur over the lifespan must also be considered amidst ongoing efforts to distinguish between rapists and rapes. Variation in the expression of sexually aggressive behavior over time suggests that prevention efforts should be implemented at multiple time points. Research is needed to determine the most efficacious combination of universal and targeted interventions, and to understand how strategies – such as bystander intervention and norms correction – can best be tailored to subgroups of men.

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Efficacy of hand washing and nail clipping on parasitic infection

Mahmud MA, Spigt M, Bezabih AM, Pavon IL, Dinant GJ, Velasco RB. Efficacy of Handwashing with Soap and Nail Clipping on Intestinal Parasitic Infections in School-Aged Children: A Factorial Cluster Randomized Controlled Trial. *PLoS Med* (2015). doi: 10.1371/journal.pmed.1001837.

Question Among children without parasites in Ethiopia, what is the therapeutic benefit of hand washing and/or nail clipping in preventing parasitic infestation?

Design 2 X 2 cluster factorial randomized controlled trial.

Setting Rural northern Ethiopia.

Participants 367 school-aged children (aged 6–15 years) from 216 randomized households.

Intervention Hand washing with soap and/or nail clipping or neither.

Outcomes Parasitic infection rate (primary) and anemia (secondary).

Main Results Odds of parasite reinfection was lower both for hand washing (adjusted odds ratio [AOR] 0.32, 95% CI: 0.17 to 0.62) and nail clipping (AOR 0.51, 95% CI: 0.27 to 0.95). Hand washing also was protective against anemia (AOR 0.39, 95% CI: 0.20 to 0.78), but the difference for nail clipping was not statistically significant (AOR 0.53, 95% CI: 0.27 to 1.04).

Conclusions Hand washing with soap and weekly nail clipping significantly decreased intestinal parasite infection rates.

Commentary This study offers important evidence of the efficacy of potentially scalable interventions to prevent parasite infection and anemia within a vulnerable population. This evidence is particularly important given renewed questions about the effectiveness of drug-based strategies such as school deworming.¹ Moreover, although hand washing with soap is widely promoted, its effectiveness against diarrhea—a major killer of young children—has been questioned in a systematic review that adjusted trial results for nonblinding.² By relying on objective outcomes, this study overcomes this potential reporting bias. The study also provides evidence

of the efficacy of fingernail clipping—an intervention that has not previously been investigated. However, as the authors note, the intervention was intensive and its potential to be rolled out at scale is unclear, given its cost and sustainability and effects over periods beyond the six-month follow-up period. Although the study focused on parasite infection and anemia, it might have also reported on respiratory infection and diarrhea—diseases that represent a much larger burden of disease. Although the authors cite low levels of parasite prevalence, it is not clear why they did not at least report on the intensity of infection, a stipulated outcome in the protocol and one that may be more highly correlated with adverse health outcomes in young children.³

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Multivariate survival factors in congenital heart disease

Danford DA, Martin AB, Danford CJ, Kaul S, Marshall AM, Kutty S. Clinical Implications of a Multivariate Stratification Model for the Estimation of Prognosis in Ventricular Septal Defect. *J Pediatr*. 2015;167:103-7.

Question Among children with ventricular septal defect (VSD), what are the multivariate prognostic factors associated with survival, free from intervention (SFFI)?

Design Prospective, observational multivariate-prognosis derivation and validation cohort study.

Setting Cardiology outpatient clinics in Omaha and Lincoln, Nebraska, and Boston, Massachusetts.

Participants Children with congenital heart disease, followed prospectively up to 10 years.

Intervention Need for surgical or catheter-mediated intervention.

Outcomes SFFI.

Main Results The key multivariate factors were degree of pathophysiology, VSD location, interventional history, and secondary cardiac defects. Six strata were defined, the most favorable predicting nearly 100% SFFI at 10 years, and the least favorable, a high likelihood of an event within weeks.

Strata with best SFFI had many subjects with nearly normal physiology, muscular VSD location, or prior intervention.

Conclusions A prediction model for SFFI in VSD has been derived and validated.

Commentary Risk-stratified prognosis is critical to improving the quality of care for children with congenital heart disease. The Society of Thoracic Surgeons and others have begun to develop empiric risk models predicting post-operative morbidity and mortality.^{1,2} Similar tools do not yet exist to predict the need for intervention. The authors' secondary aim, to demonstrate proof of concept of a risk stratification model for SFFI among pediatric congenital heart disease generally, is important and well accomplished. The cohorts employed, however, limit the applicability of this particular VSD model. The authors included patients who both had and had not undergone previous interventions, as well as large numbers of older children, well past the typical age of symptomatic presentation. The mean age in the derivation cohort was 4.0 years. Over a mean follow-up of 4.4 years, only 9% of these children required intervention. Although the validation cohort was somewhat younger, the mean age was 1.6 years – well beyond the typical symptomatic window. Median ages were not reported. Large numbers of older patients with hemodynamically insignificant VSDs inflated the c-statistic (how well the model can discriminate between observations at different levels of the outcome). The question is not whether a model can predict SFFI in children who have already proven that they do not need intervention, but rather, for those whom we do not yet know the answer. Even though the authors are to be applauded for their bold start in tackling this important topic, it should be retested in a younger patient cohort with VSDs of uncertain hemodynamic significance.

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Pimecrolimus is safe and effective in treating atopic dermatitis

Sigurgeirsson B, Boznanski A, Todd G, Vertruyen A, Schutelaar ML, Zhu X, et al. Safety and efficacy of pimecrolimus in atopic dermatitis: a 5-year randomized trial. *Pediatrics*. 2015;135:597-606.

Question What is the relative safety and therapeutic benefit of pimecrolimus (PIM), compared with topical corticosteroids (TCS), in long-term treatment of infantile atopic dermatitis (AD)?

Design Randomized controlled 5-year, open label trial.

Setting Multicenter, international study.

Participants Infants, 3-12 years old at study entry, with mild-moderate AD.

Intervention PIM versus TCS, with TCS use for flares in both groups.

Outcomes Safety and long-term outcome.

Main Results Patients in the PIM group used TCSs for a median of only 7 days (Q1: 0, Q3: 49 days) compared with 178 days (Q1: 77, Q3: 396 days) in the TCS group. Adverse events were similar in both groups without evidence for impairment of immunity. Treatment success after 3 weeks was similar: absolute risk reduction -2.1% (95% CI, -6.1 to 1.9%).

Conclusions PIM and TCS were equally safe and effective.

Commentary This study was a well-designed, open-label, parallel-group, “real-world” design randomized clinical trial, addressing the efficacy and safety of PIM 1% cream in infants over a multiyear period. Both PIM and TCS had similar safety and efficacy, immunological competency, and frequency of adverse events, although PIM use showed a small statistical increase of certain infections (bronchitis and infected eczema). Similar to a recently published cohort registry study, PIM therapy showed no increase in lymphoma or skin cancers.¹ Also, independent of topical calcineurin inhibitor use, atopic dermatitis severity is a recognized risk factor

for lymphoma.² Limitations to the study include intermittent use of PIM, though this is consistent with the “real world,” and lack of comparison with mid-strength TCS. Although TCS are still considered first-line therapy, this study adds reassuring data that PIM is safe and efficacious. The conclusions also are consistent with recently published guidelines for the management of atopic dermatitis from the American Academy of Dermatology stating that off-label use of topical calcineurin inhibitors may be recommended for children under 2 years of age based upon a significant database of efficacy and safety.³

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