

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: SYSTEMATIC REVIEW, PART 2, META-ANALYSIS (MA): A systematic review is a methodologically rigorous overview of the medical literature designed to answer a specific clinical question. MA is the statistical application to a systematic review's individual studies' combined results. There are 2 basic approaches to combining individual-study results: combining individual patient data and combining individual study-summary data using weighted averaging. The latter is notably more common, as individual patient results across multiple studies is difficult to obtain. What emerges from the MA results is essentially a single, larger “study” with more statistical power and a more precise effect estimate. Perhaps the most important underlying problem in MA is assuming that the individual studies' methodologies are sufficiently identical. In other words, are the individual studies' results measuring the identical or almost-identical effect? To answer this, statistical methods provide an estimate of heterogeneity (the less heterogeneity, the more reliable the final MA summary result). One such method is the I test, discussed in an earlier EBM Pearl.¹ Among the various controversies surrounding MA is the realization that an MA result and a result from an equivalently-large (study patients), well-designed single study—on the exact same clinical question—may not be numerically the same and have differing clinical implications. The controversy lies in which approach—an MA or a large study—is a better estimate of the “true” result. In any case, MA, a methodologically-rigorous, statistically well-powered, enhanced-precision numeric-effect summary of the entire literature on a single clinical question, affords clinicians a tool to inform clinical decision making, in the hope that patients are better served thereby.

APPLICATION/TRANSLATION PEARL: THE CLINICIAN AND DECISION MAKING: “EBM is a systematic approach to clinical problem solving which allows the integration of the best available research evidence with clinical expertise and patient values.”² This Application/Translation Pearls installment continues the discussion of the third leg of the EBM definition: “patient values.” The previous Pearl discussed patient values from the perspective of the patient. We will now consider a broader definition of “patient values”—“patient-clinician values”—bringing the clinician within the definition of “patient.” The point here is that both patient and clinician, within the context of their knowledge, temperament, value system, and a host of external influences, are affected by the clinical problem. An expert clinician recognizes that skillful clinical-literature appraisal is not the sole criterion in rendering a clinical decision for their patient. They recognize that many factors may need consideration: the accuracy of their clinical literature appraisal, the accuracy of the literature's solution to their patient's problem, an accurate assessment of their clinical expertise, their personal level of risk aversion (especially within the context of a novel result in the literature), their level of personal virtue (arrogance, eg, asking for help), empathy, dedication to their patient, integrity), their desire to rely on “official” medical-society recommendations, clearly understanding their patient's personal context, their responsibility to their next patient in a busy clinic or inpatient unit. Certainly, not in all clinical contexts are these issues germane: a positive strep screen in a non-toxic-appearing patient with pharyngitis does not invoke much decision complexity beyond the patient's personal context. However, the more complex the clinical problem, the more rapidly these other “patient-clinician values” impose, or should impose themselves into the clinical decision process. The currently emerging clinical-decision research focuses on a number of these “patient-clinician values.”

—Jordan Hupert, MD

References

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2. Sackett DL, Strauss SE, Richardson WS, Rosenberg W, Haynes RB. *Evidence-based medicine: how to practice and teach EBM*. London: Churchill-Livingstone; 2000.

Narrow-spectrum, compared with broad-spectrum, antibiotics equally effective with less adverse events

Gerber JS, Ross RK, Bryan M, Localio AR, Szymczak JE, Wasserman R, et al. Association of Broad- vs Narrow-Spectrum Antibiotics With Treatment Failure, Adverse Events, and Quality of Life in Children With Acute Respiratory Tract Infections. *JAMA* 2017;318:2325-36.

Question Among children with acute respiratory infections (acute otitis media, group A streptococcal pharyngitis, and acute sinusitis), what is the efficacy and safety profile of broad-spectrum, compared with narrow-spectrum, antibiotics?

Design Retrospective and prospective cohorts. Stratified and propensity score-matched analyses.

Setting Thirty-one pediatric practices in Pennsylvania and New Jersey.

Participants Children 6 months to 12 years, with acute otitis media, group A streptococcal pharyngitis, and acute sinusitis.

Intervention Broad- versus narrow-spectrum antibiotics.

Outcomes Effectiveness and adverse events.

Main Results Broad-spectrum antibiotics were not associated with less treatment failure, risk difference 0.3% (95% CI, -0.4% to 0.9%), and were associated with more clinician-reported and patient-reported adverse events, risk difference 1.1% (95% CI, 0.4% to 1.8%) and 12.2% (95% CI, 7.3% to 17.2%), respectively.

Conclusions Narrow-, compared with broad-spectrum antibiotics were equally effective and demonstrated a lower rate of adverse events.

Commentary This cohort study supports guidelines recommending narrow-spectrum amoxicillin or penicillin for treatment of acute otitis media, acute sinusitis, and group A streptococcal pharyngitis in children. Although broad-spectrum antibiotics, such as amoxicillin-clavulanate, are commonly prescribed based on conflicting guidelines for these conditions, they were not associated with improved outcomes compared to narrow-spectrum therapy. This large retrospective cohort demonstrated convincingly that broad-spectrum antibiotics do not lower overall rates of treatment failure, even when adjusting for differences in provider prescribing practices or illness severity using clinician-stratified and propensity-score matched analyses. The unique inclusion of patient-reported outcomes in a prospective cohort detected a 10-fold higher rate of adverse events compared with the retrospective cohort, which suggests most antibiotic adverse events are unreported and/or unrecognized by clinicians. Also, in this group, broad-spectrum antibiotics were associated with an increased risk of adverse events with no improvement in quality of life. While observational cohorts undoubtedly include children with viral infections that may obfuscate differences in antibiotic efficacy, this study reflects real clinical practice where the empiric choice of broad rather than narrow-spectrum antibiotics for acute respiratory infections in children may lead to more harm than benefit.

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Probiotic *Lactobacillus reuteri* effective in treating infantile colic and is associated with inflammatory marker reduction

Savino F, Garro M, Montanari P, Galliano I, Bergallo M. Crying Time and ROR γ /FOXP3 Expression in *Lactobacillus reuteri* DSM17938-Treated Infants with Colic: A Randomized Trial. *J Pediatr* 2018;192:171-7.e1.

Question Among infants with infantile colic, what is the therapeutic efficacy of *Lactobacillus reuteri* (LR), compared with placebo, in reducing crying?

Design Randomized controlled trial.

Setting Turin, Italy.

Participants Infants <2 months of age with infantile colic.

Intervention LR compared with placebo.

Outcomes Crying time.

Main Results Infants receiving LR demonstrated significantly less crying after one month of treatment, number needed to treat to reduce crying by 50%, 3 (95% CI, 2-5). Inflammatory markers were significantly reduced in patients treated with LR.

Conclusions LR was effective in ameliorating crying in infants with infantile colic.

Commentary Emerging evidence suggests that colic may be more than a behavioral “extreme.” Previous studies by Savino et al suggest that colic is associated with an abnormal microbial population, and we later found evidence for gut inflammation, as evidenced by high fecal calprotectin.¹ Inflammation in the gut, linked to dysbiosis (microbial imbalance), could explain the elevated calprotectin and eventual resolution as the infant’s microbial richness increases from scanty at birth, to richer at 4-6 months, and to full richness at 3 years of age. Certain microbes, such as Clostridia and Lactobacilli, and especially LR, act to enrich the population of intestinal anti-inflammatory T cells (“regulatory T cells” or Tregs) in rodents.² The difference in the change in calprotectin in this study was due to a higher baseline value in the LR group than in the placebo group, but Partty et al also showed that infants with colic had increased blood concentrations of inflammatory chemokines IL-8, MCP-1, and MIP-1 β .³ It is unclear why Savino et al did not look at Tregs using established living cell flow cytometry FOXP3 staining or a Th1 or Th2 cell marker, but clearly the results showed that LR but not placebo enhanced the expression of FOXP3 without a change in inflammatory T helper cell-17 (Th17) marker ROR-gamma. The Savino et al study exemplifies excellent recruitment and retention while adding information regarding mechanism. They have once again linked the improvement in crying time with reduced calprotectin and probably increased Tregs. In future studies, quantitation of the percentage of the 4 major classes of circulating T cells

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