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: THE META-ANALYSIS I^2 STATISTIC: A primary meta-analysis validity issue is combining studies that are measuring the same outcome in the same way. At times, individual study results may vary considerably. This variability may be due to clinical and methodological study differences. The I^2 statistic was developed to measure outcome variability among the individual studies. The higher the variability (heterogeneity), the more likely the individual studies are insufficiently similar and therefore should not be combined. As a general rule, an I^2 <40% suggests homogeneity, which supports study combination. Larger values represent a higher likelihood of heterogeneity and suggest that meta-analysis may not be warranted. An example of how the I^2 is used in a meta-analysis is shown in the piece by Zhang on page 221 regarding the article by Brooks et al (*JAMA Pediatr* 2016;170:577-84).

LITERATURE SEARCH PEARL: SUMSEARCH 2: SUMSearch 2 (http://sumsearch.org), developed by Dr Robert Badgett, is a free, University of Kansas-based meta-search engine designed to perform multiple searches at one time, employing a number of other Internet-based medical-literature search engines, and collating the results in one place. The SUMSearch 2 standard 6 search iterations enhance the search quality, retrieving the most methodologically sound studies, and grouping them by original studies, systematic reviews, and guidelines. SUMSearch 2 also displays current medical news and ClinDx (clindx.wordpress.com), a blog that highlights studies that compute clinical exam diagnostic test statistics.

—Jordan Hupert, MD

Hypertonic saline for bronchiolitis – a meta-analysis reanalysis

Brooks CG, Harrison WN, Ralston SL. Association Between Hypertonic Saline and Hospital Length of Stay in Acute Viral Bronchiolitis: A Reanalysis of 2 Meta-analyses. *JAMA Pediatr* 2016;170:577-84.

Question Among hospitalized infants with bronchiolitis, what is the therapeutic efficacy of hypertonic saline (HS), compared with placebo, in reducing length of stay (LOS)?

Design Re-analysis of 2 meta-analyses of randomized controlled studies.

Setting Hospitals worldwide.

Participants Mean age <9 months.

Intervention HS versus placebo.

Outcomes LOS and study heterogeneity as measured by the I^2 statistic.

Main Results Two main sources of heterogeneity were identified. Controlling, either for one study population with a widely divergent primary outcome definition, or, for divergent, between-treatment-groups prepresentation mean day of illness (DOI), resolved the heterogeneity: I^2 reduced from 78% to 45% and 0%, respectively, and produced nonsignificant summary estimates (ie, HS does not affect LOS).

Conclusions An outlier population and unbalanced treatment groups confounded previous HS meta-analyses' results.

Commentary The substantial heterogeneity of LOS could be expected given the variation across trials in definition of acute bronchiolitis, disease severity, standard care, intervention regimen, outcome measures and risk of bias. This and other recently published systematic reviews have explored such potential heterogeneity sources.[1-3] One of the main sources of heterogeneity identified by this review was the outlier results of two trials from the same group in China. These two trials used more stringent discharge criteria and had longer LOS in the control groups. Another main source of heterogeneity identified by this review was an imbalance in the mean DOI at presentation between treatment groups. However, caution should be taken in interpreting this finding. First, a difference of 0.5-day in DOI is an arbitrary cut-off for classifying subgroups. Any changes in the cut-off value may substantially affect the results of analysis. Second, it does not seem reasonable to combine, into the same subgroup, five trials that did not report DOI, two trials with a group difference of ≥0.5 day in DOI, and three trials with a balanced DOI. Given that neither individual trials nor pooled estimates from systematic reviews could definitively confirm or deny the potential benefits of HS in acute bronchiolitis, large international multicenter trials are still warranted.

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2. Maguire C, Cantrill H, Hind D, Bradburn M, Everard ML. Hypertonic saline (HS) for acute bronchiolitis: systematic review and meta-analysis. BMC Pulm Med 2015;15:148.
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Abscess drainage with and without antibiotics

Talan DA, Mower WR, Krishnadasan A, Abrahamian FM, Lovecchio F, Karras DJ, et al. Trimethoprim-Sulfamethoxazole versus Placebo for Uncomplicated Skin Abscess. *N Engl J Med* 2016;374:823-32.

Question Among children with an uncomplicated abscess, what is the therapeutic efficacy of trimethoprim-sulfamethoxazole (TMPS) compared with placebo, in abscess resolution?

Design Multicenter, randomized, controlled trial.

Setting Outpatient clinic.

Participants Patients, 14-73 years old of age with a drainable abscess.

Intervention Drainage plus TMPS or placebo.

Outcomes Abscess resolution 7-14 days following treatment.

Main Results The absolute risk reduction for abscess resolution with TMPS was 6.9% (95% CI, 2.1%-11.7%), number needed to treat, 15 (95% CI, 9-48). Antibiotic treatment was also associated with statistically significant lower rates of subsequent surgical drainage (3.4% vs 8.6%), new skin infections (3.1% vs 10.3%), and infections of household members (1.7% vs 4.1%).

Conclusions TMPS use improved cure rates compared with drainage alone.

Commentary Historically, uncomplicated skin-abscess first-line treatment has been surgical drainage, resulting in resolution in approximately 80% of cases.[1] Treatment with antibiotics, both compared with drainage alone and concomitant drainage plus antibiotics, has not been previously shown to improve cure rates. However, many of these studies were performed prior to increasing rates of community acquired MRSA and limited by small patient populations.[1,2] The current study by Talan et al, which is both well-designed and adequately powered, provides new evidence as to the efficacy of adjuvant antibiotic treatment of skin abscesses. These results should be interpreted with caution, as a significant number of abscesses (73.6%) were cured with drainage alone. Improvements in cure rate, new infections, and repeat drainage were modest. Gastrointestinal side effects of antibiotics treatment were mild and there were no serious adverse events, such as *Clostridium difficile* colitis or Stevens Johnson syndrome. This study, in conjunction with another study,[3] suggests the cost-benefit ratio for antibiotics in the treatment of soft tissue infections may be changing.

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Antibiotic treatment of appendicitis

Sallinen V, Akl EA, You JJ, Agarwal A, Shoucair S, Vandvik PO, et al. Meta-analysis of antibiotics versus appendicectomy for nonperforated acute appendicitis. *Br J Surg* 2016;103:656-67.

Question Among children with nonperforated appendicitis, what is the therapeutic efficacy of antibiotic treatment, compared with prompt appendectomy, in resolving appendicitis?

Design Meta-analysis of randomized trials.

Setting Europe.

Participants Children, young adults, and adults, 5-75 years old.

Intervention Antibiotic treatment versus prompt appendectomy.

Outcomes Complications and appendicitis relapse.

Main Results No difference in complication rate. Within 1 year, appendicitis recurred in 114 of 510 patients in the antibiotic group: pooled estimate 22.6% (95% CI, 15.6% to 30.4%), number needed to recur: 5 (95% CI, 4 to 6).

Conclusions Nonperforated appendicitis antibiotic treatment is a value- and preference-based decision.

Commentary This meta-analysis is meticulously performed and introduces both Grading of Recommendations Assessment, Development and Evaluation for assessing the quality of evidence, and the Clavien-Dindo classification for stratification of complications. Surprisingly, there are now more meta-analyses published than randomized controlled trials, and even a review of the meta-analyses.[1] All meta-analyses include a different combination of studies but come to fairly similar conclusions, raising the question of the benefit of yet another meta-analysis. That said, this meta-analysis provides the best presented, and probably best quality data to present to the individual patient for shared decision-making. Still, long-term outcome data are needed to reach a final conclusion regarding the benefit of the nonoperative approach to acute appendicitis. My personal opinion is that the antibiotics-first, appendectomy-when-needed treatment strategy of nonperforated acute appendicitis in children is valid in cases where surgery, and general anesthesia, would mean an increased risk (eg, post gastroschisis, omphalocele, or other previous major abdominal surgery, ongoing airway infection, and in patients with cystic fibrosis). Apart from this, nonoperative treatment should not routinely be performed outside the framework of a randomized controlled trial.