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* and *The Journal of Pediatrics*, and from customized EvidenceUpdates alerts.

EVIDENCE-BASED MEDICINE PEARL: INTENTION TO TREAT (ITT): ITT is an important methodological validity issue of a clinical therapeutic study. ITT can be summarized as "analyze what you randomize" —even if patients do not take their assigned therapy or drop out of the study. The purpose of ITT methodology is to mirror typical, real-life clinical conditions. For example, consider a two-group, parallel-design, randomized controlled trial comparing amoxicillin and placebo for the treatment of otitis media. A number of the patients randomized to the amoxicillin group never take the amoxicillin. Simple logic may suggest that either those patients should be removed from analysis or switched to the placebo group. ITT requires these patients to be analyzed in the amoxicillin group because patients do not always take their medicine, and they do not always follow-up. Outcome measures (eg, number needed to treat) are derived from these real-life groups, and are therefore reflective of what is likely to occur in the real-life clinical venue.

SEARCHING PEARL: ADVANCED USE OF PUBMED—ANNE O'TATE: PubMed is a free, US-government-supported search and retrieval system of the MEDLINE biomedical database. Since PubMed's debut, a number of programs have been developed to organize PubMed results in a user-friendly manner. Anne O'Tate is one of those programs, designed to identify and summarize key features of the most relevant articles. Anne O'Tate (http://arrowsmith.psych.uic.edu/cgi-bin/arrowsmith_uic/AnneOTate.cgi) is a free service that offers a number of ways to organize one's PubMed search to facilitate specific topic retrieval or specific field browsing. Examples include: (1) "important words"—organizes the retrieved articles by words that occur more frequently in the literature retrieved, than in PubMed generally, thus identifying a lexicon specific to the literature retrieved; (2) "topics" organizes by medical subject headings (MeSH terms); and (3) "cluster by function"—organizes by larger topics (from the MeSH terms), generating themes and allowing the user to gain a quick overview of the retrieved literature.

—**Jordan Hupert, MD**

Urokinase and VATS are equally effective for septated empyema

Marhuenda C, Barcelo C, Fuentes I, Guilln G, Cano I, Lopez M, et al. Urokinase Versus VATS for Treatment of Empyema: A Randomized Multicenter Clinical Trial. *Pediatrics.* 2014;134:e1301-7.

Question Among children with septated empyema, what is the therapeutic efficacy of drainage and urokinase compared with video-assisted thoracoscopic surgery (VATS), as measured by post-treatment length of hospital stay (LOS)?

Design Randomized, controlled, multicenter study.

Setting 6 university hospitals in Spain.

Participants Previously healthy children <15 years old with septated empyema.

Intervention Drainage and urokinase vs VATS.

Primary Outcome Post treatment LOS.

Main Results No statistically significant differences were found between drainage and urokinase and VATS in the median postoperative stay (10 vs 9 days).

Conclusions Drainage plus urokinase instillation is as effective as VATS for first-line treatment of septated empyema.

Commentary All currently available treatment options for childhood empyema are effective and safe, and most children make a complete recovery irrespective of the intervention received. This has led to inherent center or physician bias in the primary treatment of choice. Marhuenda et al, report that intrapleural urokinase and VATS were equally efficacious as primary treatment options for septated empyema in children. Similarly, previous prospective studies also state clinical equipoise between intrapleural fibrinolytics and VATS.[1-3] However, this study did not measure important outcomes such as the amount of pain associated with the intervention, long-term pulmonary function, and exercise tolerance. Nevertheless, being a multicenter trial, perhaps the results from this trial are more extrapolatable—particularly as only patients with effusions in ultrasonographic stages 2 and 3 were included. Although this study further strengthens evidence in favor of intrapleural urokinase as the primary treatment for childhood empyema, a multicenter equivalence study comparing the two interventions, inclusive of outcomes other than hospital stay, will lay the case to rest.

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Demonstration of placebo effect for nonspecific cough medicine

Paul IM, Beiler JS, Vallati JR, Duda LM, King TS. Placebo effect in the treatment of acute cough in infants and toddlers: a randomized clinical trial. *JAMA Pediatr*. 2014;168:1107-13.

Question Among children with nonspecific cough, what is the therapeutic efficacy of placebo, compared with no treatment, in reducing cough frequency?

Design Randomized, controlled trial.

Setting Two university affiliated outpatient clinics in Pennsylvania, US.

Participants Infants 2-47 months of age with nonspecific acute cough duration of 7 days or less.

Interventions (1) Pasteurized agave nectar; (2) natural grape-flavored water with caramel color (placebo); and (3) no treatment.

Primary Efficacy Measure Change in cough frequency between the first night and the end of the second night.

Main Results Significant differences in symptom improvement were detected between the study groups, with agave nectar and placebo proving to be superior to no treatment, but no significant differences for any outcome were found when comparing agave nectar against placebo.

Conclusions In a comparison of agave nectar, placebo, and no treatment, a placebo effect was demonstrated, with no additional benefit offered by agave nectar.

Commentary This high-quality randomized-controlled trial demonstrates that agave nectar and placebo were superior to no treatment in relieving nonspecific cough in children aged 2 to 47 months. However, no significant differences were detected between the agave nectar and placebo groups. Eccles suggests four different effects to antitussive medicine: pharmacological, physiological, true placebo, and nonspecific effects.[1] The pharmacological effect is related to the active ingredient of the medicine. The physiological effects can be attributed to physical properties of the medicine such as taste, smell, viscosity, acidity, texture, and temperature. A true placebo effect refers to the psychological therapeutic effect of the treatment, and it depends on the belief in the effectiveness of the treatment and the attitude of the patient towards the therapist. Nonspecific effects included the natural (spontaneous) recovery from the illness. Lee et al also demonstrate that placebo treatment has significant antitussive activity in adult patients.[2] In clinical trials where a "no treatment" group is included, it is possible to control for any nonspecific effects of treatment by subtracting changes in the no treatment group from the changes observed in the placebo and treatment groups. Parents and physicians want symptomatic relief of cough associated with upper respiratory tract infections. If a placebo is low cost, has no or minimal adverse effects, and it can reduce unnecessary antibiotic treatment, it appears to be a preferable treatment option.[3]

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Limited efficacy of antigastroesophageal reflux medications in children

Tighe M, Afzal NA, Bevan A, Hayen A, Munro A, Beattie RM. Pharmacological treatment of children with gastro-oesophageal reflux. *Cochrane Database Syst Rev*. 2014;11:CD008550.

Question Among children with gastroesophageal reflux (GER), what is the therapeutic efficacy of acid suppressant medications, compared with placebo, in resolving signs and symptoms of acid reflux?

Design Systematic review.

Setting Various inpatient and outpatient settings.

Participants Children from birth to 16 years of age with signs and/or symptoms of GER.

Intervention Various antireflux medications.

Outcomes Improvement in clinical GER signs and/or symptoms.

Main Results Based on moderate-level evidence, proton pump inhibitors (PPIs) reduce GER symptoms in children with confirmed erosive esophagitis. Some evidence suggests H2 blockers adequately treat GER symptoms. For both classes of drugs, the effects are only in older children. In infants, moderate evidence indicates that Gaviscon Infant (sodium alginate, magnesium alginate, mannitol; Reckitt-Benckiser Healthcare, Slough, England) improves symptoms.

Conclusions In pediatric patients with GER, there is mild to moderate evidence supporting the use of PPIs and H2 antagonists in older children, and Gaviscon Infant in infants.

Commentary GER is common among infants and children, with prevalence as high as 30%-67%.[1,2] At this frequency of