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: THE EBM PROCESS AND READING THE METHODS SECTION: VALIDITY OF THERAPEUTIC STUDIES: Understanding the primary clinical literature includes reading the Methods section (not only the title and conclusions!) to assess most, if not all, of the study's validity. Assessing a study's validity is the fourth step of the basic 6-step EBM process: patient, question, search, validity, results, and patient application. Each study type has its own set of validity issues (often expressed as questions). A therapeutic study's 4 primary validity issues are: (1) Was the study randomized?; (2) Was patient follow-up sufficiently long and complete?; (3) Were patients analyzed in the groups to which they were randomized (intention to treat)?; and (4) Were patients and clinicians blinded to the treatment allocation? Previous EBM Pearls discussed questions 1 and 3 (*J Pediatr* 2015;166:777 and 1320). A satisfactory positive answer to question 2 assures that the study was sufficiently long to manifest an outcome risk reduction (if one occurs) from a new therapy, and accounts for all patients (missing/unaccounted patients may have dropped out for nonrandom, outcome-affecting reasons). A satisfactory positive answer to question 4 reduces outcome-affecting bias due to patient and clinician group-assignment knowledge.

LITERATURE SEARCH PEARL: MEDEDPORTAL: MedEdPORTAL (www.mededportal.org) is an Association of American Medical Colleges (AAMC)-sponsored, peer-reviewed, health education resource repository. It includes curricula, lectures, protocols, cases, assessments and other health-education-related materials and tools. MedEdPORTAL's primary focus is medical education. However, many health disciplines (eg, dentistry, nursing, pharmacy) are represented, as are all levels of health education. The MedEdPORTAL database is free, searchable, and materials may be downloaded. MedEdPORTAL also includes a nonpeer-reviewed section (iCollaborative) and a continuing education directory (CE Directory).

—Jordan Hupert, MD

Long-acting beta agonists do not increase serious asthma-related event risk

Stempel DA, Szefler SJ, Pedersen S, Zeiger RS, Yeakey AM, Lee LA, et al. Safety of Adding Salmeterol to Fluticasone Propionate in Children with Asthma. *N Engl J Med* 2016;375:840-9.

Question Among children with asthma, what is the hospitalization risk of the long-acting beta-agonist (LABA) salmeterol plus fluticasone, compared with fluticasone alone?

Design Randomized, controlled trial.

Setting 567 trial centers in 32 countries.

Participants Children with asthma, 4 to 11 years old.

Intervention Fluticasone propionate plus salmeterol or fluticasone alone.

Outcomes A composite end point including death, endotracheal intubation, and hospitalization.

Main Results The absolute risk increase for a serious asthma-related event (all were hospitalizations) was 0.19%, (95% CI, –0.24%-0.63%).

Conclusions Salmeterol did not increase risk over fluticasone alone.

Commentary This trial assessed the safety of a fixed-dose combination of fluticasone and salmeterol in children with persistent asthma to address the concerns raised by the US Food and Drug Administration.[1] The study outcomes align with those reported in our Cochrane systematic review evaluating the safety and efficacy of add-on LABA in children with asthma.[2] There was no statistically significant reduction in the risk of hospitalization with a combination of fluticasone-salmeterol as compared with fluticasone alone. We reported that add-on LABA failed to reduce the risk of hospital admissions (RR 1.74, 95% CI, 0.90-3.36; 1292 children) as compared with the same dose of inhaled corticosteroids. Interestingly, compared with inhaled corticosteroids, irrespective of dose, add-on LABA doubled the risk of hospitalization (RR 1.90, 95% CI, 1.06-3.40; 2060 children). Moreover, except in lung function tests and rescue therapy use, we did not find additional benefits of using add-on LABA on other markers of efficacy and safety, a finding that warrants further evaluation.

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References

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2. Chauhan BF, Chartrand C, Ni Chroinin M, Milan SJ, Ducharme FM. Addition of long-acting beta2-agonists to inhaled corticosteroids for chronic asthma in children. Cochrane Database Syst Rev 2015;(11):CD007949.

Ibuprofen use in viral infection is associated with subsequent empyema

Le Bourgeois M, Ferroni A, Leruez-Ville M, Varon E, Thumerelle C, Brémont F, et al. Nonsteroidal Anti-Inflammatory Drug without Antibiotics for Acute Viral Infection Increases the Empyema Risk in Children: A Matched Case-Control Study. *J Pediatr* 2016;175:47-53.

Question Among children with viral infection, what is the association of nonsteroidal anti-inflammatory drug (NSAID) use and subsequent empyema development?

Design Matched case control.

Setting 15 French pediatric respiratory centers.

Participants Children 3 months to 15 years old with empyema and matched controls with a viral infection.

Intervention NASAID use or not.

Outcomes Empyema.

Main Results Increased empyema risk was associated with NSAIDs use: adjusted OR 2.79 (95% CI, 1.4-5.58); and decreased risk with antibiotic use: adjusted OR 0.32 (95% CI, 0.11-0.97).

Conclusions NSAID and antibiotic use in viral infections were associated with an increased and decreased risk of subsequent empyema, respectively.

Commentary This case control study adds to several prior observational studies referenced in the report on the relationship between NSAID use and septic complications, which are plausibly due to the suppression of the body's inflammatory response to infection. The strength of the current study is the careful exclusion criteria for cases to ensure that reverse causality is not operating. The main limitations are the retrospective clinical assessment and possible recall bias and residual confounding by indication. However, two pieces of evidence from randomized trials support the causal inferences: the Pragmatic trial of Ibuprofen, Paracetamol and Steam (PIPS) trial,[1] which demonstrated an increase in both reconsultations with progression of symptoms and also an increase in complications among those advised to use regular ibuprofen; and the Internet Doctor trial,[2] which found worse control of severe symptoms attributable to advice to use ibuprofen. The balance of evidence currently suggests that NSAIDs either should not be used at all in acute respiratory infections or perhaps used very sparingly at particularly difficult times for symptom control—such as to help get a night's sleep when acetaminophen alone is not controlling symptoms.

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2. Little P, Stuart B, Andreou P, McDermott L, Joseph J, Mullee M, et al. Primary care randomised controlled trial of a tailored interactive website for the self-management of respiratory infections (Internet Doctor). BMJ Open 2016;6:e009769.

US Preventive Task Force cites insufficient evidence for pediatric lipid screening

Bibbins-Domingo K, Grossman DC, Curry SJ, Davidson KW, Epling JW Jr, García FA, et al. Screening for Lipid Disorders in Children and Adolescents: US Preventive Services Task Force Recommendation Statement. *JAMA* 2016;316:625-33.

Question What is the association of pediatric lipid screening with prevention of adult cardiovascular disease or intermediate adverse outcomes and what are the harms associated with screening and treatment?

Design Recommendation statement based on a systematic review.

Setting Ambulatory settings.

Participants Asymptomatic children and adolescents, 0 to 20 years of age, without a known lipid disorder.

Intervention Routine lipid screening.

Outcomes Dyslipidemia and atherosclerosis in childhood, myocardial infarction and ischemic stroke in adulthood, and harms of screening or treatment.

Main Results There is insufficient evidence favoring benefits over risks of long-term treatment, screening, intermediate outcomes, or improvements in adult cardiovascular health outcomes.

Conclusions Current evidence is insufficient to assess the balance of benefits and harms for pediatric lipid disorder screening or treatment.

Commentary The US Preventive Task Force's (USPSTF) "I" grade ("evidence is insufficient to assess the balance of benefits and harms of screening") for universal lipid screening is unchanged from their 2007 grade, and is consistent with recommendations from the United Kingdom National Screening Committee[1] and the American Academy of Family Physicians. In contrast, the "I" grade differs markedly from previously published recommendations from a National Heart, Lung, and Blood Institute (NHLBI) expert panel, which were endorsed by the American Academy of Pediatrics (AAP).[2] The USPSTF grade is better aligned with awareness that there are costs and potential harms of lipid testing (eg, diabetes and myopathy from statin treatment), and that any benefits would be decades away and of uncertain magnitude. Had the USPSTF considered costs in their appraisal, a recommendation against screening would have been more appropriate. The majority of pediatricians are not heeding the NHLBI/AAP recommendations for universal lipid screening, likely reflecting provider intuition that scarce resources would be better utilized on higher value interventions. Rather