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: TEST-NEGATIVE DESIGN (TND): TND is a recent approach employed in estimating influenza vaccine efficacy. Compared with traditional statistical estimation in case-control or cohort studies, TND is less prone to bias from infection misclassification and to spurious results from variable healthcare-seeking behavior. Mathematically, vaccine efficacy is the same as the relative risk reduction × 100% = ([influenza rate (IR) unvaccinated patients − IR vaccinated patients]/IR unvaccinated patients) × 100% = (1 − relative risk [RR] for influenza [of vaccinated/unvaccinated]) × 100%. The resulting percentage is the relative risk of not having influenza in vaccinated/unvaccinated patients. When the overall IR is low, the RR approximates the odds ratio (OR). The OR is useful in certain cohort and in case control studies. There are some important assumptions underlying the TND approach (eg, influenza vaccine efficacy does not vary among various levels of healthcare seeking behavior), but overall, the TND is considered a robust approach in assessing influenza vaccine efficacy. An example of TND may be seen in the Jackson et al study below.

APPLICATION/TRANSLATION PEARL: CLINICAL EXPERTISE: "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."[1] The previous "Pearl" discussed the first of the 3 legs of the EBM definition, "the best available evidence." This Pearl focuses on clinical expertise. Just as the highest level of EBM practice brings the best evidence "to the bedside," the highest level of EBM practice also brings clinical expertise—at the highest possible level—"to the bedside." Verifying clinical and laboratory findings prior to assessing likelihood ratios, arriving, conclusively, at a correct diagnosis before searching for therapeutic evidence, discerning which therapeutic choices are germane to our patient's current clinical context prior to considering the magnitude of a specific number needed to treat—these are the ABCs of medical practice and are absolutely part of the EBM process. Clinical uncertainty necessitates accessing the clinical acumen of our colleagues and specialists, and all this perhaps even before formulating an answerable clinical question. Contextual patient issues such as life settings, access barriers, economic pressures, familial responsibilities—these all importantly factor into EBM decision making. Extrapolating from a study's patient population to one's own patient is not always simple or appropriate: notably outstanding evidence may fit the patient's disease but not the patient's personal or clinical context; it may even cause harm. EBM application issues constitute a field of emerging research. And even when the literature may be ample, sage, discerning clinical expertise will constitute, solidly, the second leg of the EBM practice definition.

—Jordan Hupert, MD

Reference

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

Live, attenuated influenza vaccine demonstrated ineffective

Jackson ML, Chung JR, Jackson LA, Phillips CH, Benoit J, Monto AS, et al. Influenza Vaccine Effectiveness in the United States during the 2015-2016 Season. *N Engl J Med* 2017;377:534-43.

Question Among children, what is the therapeutic efficacy of the live attenuated influenza vaccine, compared with those not receiving any influenza vaccine, in preventing influenza disease?

Design Prospective cohort during the 2015-2016 influenza season using the test-negative design.

Setting Geographically diverse US sites.

Participants Patients 6 months of age or older, with cough for 7 or fewer days.

Intervention Live attenuated influenza vaccine or none.

Outcomes Vaccine efficacy.

Main Results The live attenuated vaccine was not effective: 5% (95% CI, –47%-39%) among those who received versus those who did not receive vaccination. The inactivated vaccine was effective: 60% (95% CI, 47%-70%).

Conclusions The live attenuated influenza vaccine was not effective.

Commentary This is one of the studies that were the reason the Advisory Committee on Immunization Practices did not recommend the live attenuated influenza vaccine for the 2016-2017 season.[1] The authors analyzed the data in detail with many calculations and adjustments, all supporting the main conclusion. It is discouraging that the reason for the failure of this live attenuated vaccine during 2015-2016 is not known. Clearly, surveillance of influenza vaccine effectiveness on an annual basis needs to be continued, considering surprises and the baseline low effectiveness. The test-negative design was used in the study. If, in a group of children presenting with respiratory illness, fewer children with proven influenza have been vaccinated compared with those without influenza, it can be presumed that the vaccine prevented influenza specific illness in the proportion of the children with alternative etiologies. The quantitation of the presumed protection (effectiveness) is described and discussed in the current paper and in their reference 20.[2] This is a somewhat new technique that has appeared in the pediatric literature for only a few years and readers may wish to review it to understand how it is valid yet different from more traditional methods.

Arthur Frank, MD
University of Illinois at Chicago
Chicago, Illinois

References

1. Grohskopf LA, Sokolow LZ, Broder KR, Olsen SJ, Karron RA, Jernigan DB, et al. Prevention and control of seasonal influenza with vaccines. MMWR Recomm Rep 2016;65(RR–5):1-54.
2. Jackson ML, Nelson JC. The test-negative design for estimating influenza vaccine effectiveness. Vaccine 2013;31:2165-8.

Early-onset sepsis risk calculator reduces empiric antibiotic use

Kuzniewicz MW, Puopolo KM, Fischer A, Walsh EM, Li S, Newman TB, et al. A Quantitative, Risk-Based Approach to the Management of Neonatal Early-Onset Sepsis. *JAMA Pediatr* 2017;171:365-71.

Question Among newborns, what is the clinical benefit of an early-onset sepsis (EOS) risk calculator, compared with national guidelines, in reducing antibiotic use?

Design Cohort.

Setting Kaiser Permanente Northern California (KPNC).

Participants Neonates, 35 weeks of gestation or older.

Intervention EOS calculator or national guidelines.

Outcomes Empiric antibiotic use.

Main Results Fewer babies in the EOS calculator group experienced blood culture use: adjusted number needed to treat (aNNT) 13 (95% CI, 8 to 42), and less empirical antibiotic administration in the first 24 hours: aNNT, 56 (95% CI, 44 to 77) with no difference between 24 and 72 hours after birth and no clinical outcome differences.

Conclusions An EOS calculator reduced neonatal blood culture and empiric antibiotic use.

Commentary A liberal threshold for initiating antibiotic therapy in neonates, based on early-onset sepsis (EOS) risk factors with poor predictive value, has led to overuse of antibiotics in non-infected neonates. This contrasts starkly with the low prevalence of EOS. Antibiotic overuse early in life may have severe short-term and long-term adverse consequences.[1,2] This large cohort study from KPNC investigated clinical management of term and near-term infants with suspected or proven EOS over a 6-year period. The remarkable 50% relative reduction in antibiotic use after introduction of an EOS-calculator was not followed by a delay in therapy for infected infants or an increase in readmissions. It is evident that not only the EOS-calculator but also a bundle of co-interventions including improved patient monitoring was implemented, most likely at the same time. Moreover, the KPNC-staff must have undergone rigorous training in order to use the EOS-calculator and follow the bundle of interventions appropriately. The authors are to be congratulated for this very successful approach. The use of an EOS calculator has the potential to reduce antibiotic overuse, especially in areas where maternal risk factors, earlier, may have been over-emphasized. However, similar results may be achieved with different approaches. We recently presented data from a population-based study of 168,000 term infants in Norway over a 3-year period. In our setting, with a tradition of not recommending therapy based on risk factors alone, the proportion of term infants receiving antibiotic therapy in the first week of life was 2.3% and mortality was low.[3]

Claus Klingenberg, MD, PhD
University Hospital of North Norway
Tromsø, Norway

References

1. Esaiassen E, Fjalstad JW, Juvet LK, van den Anker J, Klingenberg C. Antibiotic exposure in neonates and early adverse outcomes — a systematic review and meta-analysis. J Antimicrob Chemother 2017;72:1858-70.
2. Bailey LC, Forrest CB, Zhang P, Richards TM, Livshits A, DeRusso PA. Association of antibiotics in infancy with early childhood obesity. JAMA Pediatr 2014;168:1063-9.
3. Fjalstad JW, Stensvold HJ, Bergseng H, Simonsen GS, Salvesen B, Rønnestad A, et al. Early onset sepsis and antibiotic exposure in term infants: a nationwide population-based study in Norway. Pediatr Infect Dis J 2016;35:1-6.

Early childhood sedentary behavior associated with worse working memory

López-Vicente M, Garcia-Aymerich J, Torrent-Pallicer J, Forns J, Ibarluzea J, Lertxundi N, et al. Are Early Physical Activity and Sedentary Behaviors Related to Working Memory at 7 and 14 Years of Age? *J Pediatr* 2017;188:35-41.e1.

Question Among primary and high school children, what is the therapeutic efficacy of early-childhood physical activity, compared with sedentary behavior, on working memory?