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: THERAPY – RESULTS: ABSOLUTE RISK REDUCTION (ARR) AND RELATIVE RISK REDUCTION (RRR): Many, if not most, therapeutic trial articles present data in a binary fashion: percent improved versus not improved in each group of the trial. Both ARR and RRR compare one group's results with the other. The ARR is the subtraction of the percentage not improved in the experimental group (experimental event rate [EER]) from the percentage not improved in the control group of the trial (control event rate [CER]). The RRR is the ARR divided by the CER. Both the ARR and RRR express the benefit of the treatment, the absolute benefit and the relative benefit, respectively. The RRR can be a bit misleading. For example, if the CER is 20% and the EER is 10%, then the ARR is 10% and the RRR is 0.5, a 50% relative risk reduction. If the CER is 0.2% and the EER is 0.1%, then the ARR is 0.1% (unlikely to be clinically significant), but the RRR is still 0.5, a 50% relative risk reduction. Remember—the inverse of the ARR is the number needed to treat (NNT).

LITERATURE SEARCH PEARL: SUMMARIES: Within the EBM clinical-applicability hierarchy (single studies, synopses of single studies, syntheses [systematic reviews and meta-analyses], synopses of syntheses, summaries, systems), "summaries" are only second to "systems." Summaries review clinical topics using EBM principles. Searching for summaries is a search for evidence on a clinical topic addressing a number of clinical questions. Two popular summary sources include UpToDate (www.uptodate.com) and DynaMed Plus (www.dynamed.com). Both of these resources are peer reviewed, have clear EBM methodology (including frequent literature searching to keep topics up to date), employ EBM-based evidence-grading systems, link to drug databases, provide continuing medical education, and include thousands of topics, including many pediatric topics. UpToDate includes graphics and is narrative in style. DynaMed Plus includes International Statistical Classification of Diseases and Related Health Problems codes, can integrate with major electronic health records, and presents topics in bulleted form. Both UpToDate and DynaMed Plus are subscription based, but many universities provide free access to their faculty and students.

—Jordan Hupert, MD

Early steroid therapy reduces Kawasaki disease coronary complications

Chen S, Dong Y, Kiuchi MG, Wang J, Li R, Ling Z, et al. Coronary Artery Complication in Kawasaki Disease and the Importance of Early Intervention: A Systematic Review and Meta-analysis. *JAMA Pediatr* 2016;170:1156-63.

Question Among children with Kawasaki disease (KD), what is the therapeutic efficacy of adjunctive corticosteroids plus intravenous immunoglobulin (IVIG) therapy compared with IVIG therapy alone, in reducing coronary complications?

Design Systematic review and meta-analysis of both randomized and non-randomized studies.

Setting Japan (most studies) and US.

Participants Children with KD.

Intervention IVIG +/− corticosteroids.

Outcomes Coronary artery size, as measure by Japanese Ministry of Health criteria or z-score.

Main Results Adjunctive corticosteroids reduced the coronary artery abnormality rate: odds ratio, 0.42 (95% CI, 0.27-0.67). Coronary abnormalities were inversely related to duration of KD prior to corticosteroids administration.

Conclusions Early adjunctive corticosteroids decrease coronary complications in patients with KD.

Commentary This meta-analysis of 16, almost exclusively Japanese, studies confirmed that adjunctive corticosteroids with IVIG for primary therapy of KD substantially improved coronary outcomes. Most benefit inured to patients predicted to be at particularly high risk for IVIG resistance and coronary abnormalities. Japanese clinicians utilize clinical scores that accurately predict patients at high risk, enabling targeted adjunctive steroid with IVIG as primary therapy.[1] Unfortunately, these clinical scores are not sufficiently sensitive or specific in multi-ethnic non-Asian populations to identify high risk patients.[2] Nevertheless, one subgroup with KD considered high risk absent an effective scoring system may be young infants <6 or perhaps <12 months old who often develop relatively severe coronary abnormalities and might benefit from adjunctive primary steroid therapy.[3] Corticosteroid as rescue therapy in IVIG nonresponders in this meta-analysis showed no significant reduction in the odds of developing coronary abnormalities compared with those receiving additional IVIG. However, this meta-analysis did not rule out whether corticosteroid rescue recipients may develop fewer severe coronary abnormalities.

Stanford T. Shulman, MD
Northwestern University
Chicago, Illinois

References

1. Kobayashi T, Saji T, Otani T, Takeuchi K, Nakamura T, Arakawa H, et al. Efficacy of Immunoglobulin plus prednisone in severe Kawasaki Disease (RAISE study). Lancet 2012;379:1613-20.
2. Sleeper LA, Minich LL, McCrindle BM, Li JS, Mason W, Colan S, et al. Evaluation of Kawasaki Disease risk–scoring systems for IVIG resistance. J Pediatr 2011;158:831-5.
3. Rosenfeld EA, Corydon KE, Shulman ST. Kawasaki Disease in infants less than one year of age. J Pediatr 1995;126:524-9.

RNA signature test to distinguish bacterial from viral infection

Herberg JA, Kaforou M, Wright VJ, Shailes H, Eleftherohorinou H, Hoggart CJ, et al. Diagnostic Test Accuracy of a 2-Transcript Host RNA Signature for Discriminating Bacterial vs Viral Infection in Febrile Children. *JAMA* 2016;316:835-45.

Question Among children, what is the diagnostic accuracy of a host RNA signature, compared with bacterial culture and viral identification testing, in detecting bacterial vs viral infection?

Design Prospective cohort: discovery and validation groups.

Setting United Kingdom, Spain, The Netherlands, and the US.

Participants Children <17 years old requiring a blood culture for presumed infection.

Intervention RNA signature.

Outcomes Bacterial or viral infection.

Main Results All 23 patients with microbiologically-confirmed bacterial infection were classified as bacterial, sensitivity, 100% (95% CI, 100%-100%) and 27 of 28 patients with definite viral infection were classified as viral, specificity, 96.4% (95% CI, 89.3%-100%).

Conclusions The RNA signature test for infection identification appears accurate.

Commentary Evaluation of acute febrile children represents a challenging situation for practicing physicians. As current bacterial identification methods have substantial limitations related to test accuracy and timeliness, recent work is now focused on host infection-response analysis.[1] Pathogens elicit distinct host responses in the blood that can be identified by using RNA signatures.[2,3] Herberg et al identified a 38-transcript, and subsequently a 2-transcript RNA signature, that discriminated children with well-defined viral and bacterial infections with high sensitivity and specificity. The next step is to validate this 2-transcript signature in larger cohorts of children with febrile illnesses caused by a variety of etiologic agents, in diverse geographic areas, and in different clinical contexts. Identification of this 2-transcript diagnostic signature will greatly facilitate the practical implementation of this technology in the clinical setting.

Octavio Ramilo, MD
Asuncion Mejias, MD, PhD
The Ohio State University
Columbus, Ohio

Prashant Mahajan, MD, MPH, MBA
University of Michigan
Ann Arbor, Michigan

Nathan Kuppermann, MD, MPH
University of California Davis
Sacramento, California

References

1. Ramilo O, Allman W, Chung W, Mejias A, Ardura M, Glaser C, et al. Gene expression patterns in blood leukocytes discriminate patients with acute infections. Blood 2007;109:2066-77.
2. Mahajan P, Kuppermann N, Mejias A, Suarez N, Chaussabel D, Casper TC, et al. Association of RNA biosignatures with bacterial infections in febrile infants aged 60 days or younger. JAMA 2016;316:846-57.
3. Tsalik EL, Henao R, Nichols M, Burke T, Ko ER, McClain MT, et al. Host gene expression classifiers diagnose acute respiratory illness etiology. Sci Transl Med 2016;8:322ra11.

M-CHAT autism screening may be inaccurate among toddlers born very preterm

Kim SH, Joseph RM, Frazier JA, O'Shea TM, Chawarska K, Allred EN, et al. Predictive Validity of the Modified Checklist for Autism in Toddlers (M-CHAT) Born Very Preterm. *J Pediatr* 2016;178:101-7.e2.

Question Among very preterm infants (<28 weeks of gestation), what is the diagnostic accuracy of the Modified Checklist for Autism in Toddlers (M-CHAT), compared with a series of autism spectrum disorder (ASD)-defining instruments, in diagnosing ASD?

Design Longitudinal, multicenter cohort of very preterm infants.

Setting US (East Coast and Midwest).

Participants 827 very preterm infants (<28 weeks of gestation) evaluated at both 2 years (M-CHAT) and 10 years of age (ASD-defining instruments).

Intervention M-CHAT.

Outcomes ASD diagnosis.

Main Results The likelihood ratio for a positive M-CHAT test (LR+) was 3.3 (95% CI, 2.4-4.4) and for a negative test (LR–) was 0.6 (95% CI, 0.4-0.8), corresponding to ASD probabilities of 20% (95% CI, 15%-25%) and 4% (95% CI, 3%-5%), respectively. The false negative and false positive rates were 48% (95% CI, 35%-61%) and 16% (95% CI, 13%-19%), respectively. Hearing and vision impairment increased false positives and negatives.