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: A CLINICAL DECISION RULE (CDR)—DERIVATION AND VALIDATION: A CDR is a combination of history and physical examination that is sufficiently diagnostically accurate, reducing the need for expensive or potentially harmful laboratory or radiologic tests. CDR development typically includes 1) a retrospective derivation set, 2) a retrospective validation set, and, eventually 3) an external validation set, where a "set" is a specific-diagnosis patient database of clinical parameters. Researchers use the derivation set to identify the diagnostic test characteristics (ie, sensitivity/specificity and/or likelihood ratios) of various history, physical exam, and simple lab test combination models compared with a gold standard. Sufficiently accurate models are then applied to a second set—either part of the original database not used in derivation or a more recent retrospective (or prospective) database. If needed, the researchers make model modifications and recalculate the diagnostic test characteristics. If the results continue to demonstrate sufficiently high diagnostic accuracy, the model is applied prospectively to at least one internal and/or one or more, external clinical sites. This edition of Current Best Evidence includes a study by Sheikh et al reporting initial results of a web-based, urinary-tract-infection CDR.

CRITICAL STATISTICAL DISTINCTION PEARL: ODDS RATIO (OR) AND RELATIVE RISK (RR): The OR and RR, both ubiquitous in the medical literature, are similar but distinct statistical concepts. RR is the disease (or other outcome) prevalence in an exposed versus non-exposed population, RR = [A/(A + B)]/[(C/C + D)] (see the 2 × 2 Table below). The OR is the disease proportion in an exposed vs non-exposed patient sample, OR = [A/B]/[C/D]. RR describes the disease prevalence ratio in specific exposed and non-exposed populations. OR describes the relative disease proportions of an exposure independent of disease prevalence. To calculate RR, you need actual prevalence data to fill in a 2 × 2 table. An OR only requires exposure information in any size sample of people with and without the disease. For example, one may only use an OR (not a RR) to describe results in case-control studies. Either may be used in cohort studies. If the disease prevalence is rare, then, mathematically, RR ~ OR, as A and C are insignificant numbers compared with B and D in the RR denominator.

	Disease	
Exposure	+	–
+	A	B
–	C	D

UTICalc may enhance UTI risk-estimation in young children

Shaikh N, Hoberman A, Hum SW, Alberty A, Muniz G, Kurs-Lasky M, et al. Development and Validation of a Calculator for Estimating the Probability of Urinary Tract Infection in Young Febrile Children. *JAMA Pediatr* 2018;172:550-6.

Question Among young children with fever, what is the diagnostic accuracy of UTICalc, compared with urine culture, in diagnosing urinary tract infection (UTI)?

Design Retrospective chart review with derivation and validation sets.

Setting Emergency department of Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania.

Participants Children 2-23 months of age with temperature >38 degrees C.

Intervention A combination of clinical and urine-analysis data modeled with logistic regression and developed into UTICalc https://uticalc.pitt.edu (accessed June 10, 2018), compared with culture.

Outcomes Culture proven UTI.

Main Results UTICalc reduced testing by 8.1% (95% CI, 4.2%-12.0%) compared with the American Academy of Pediatrics (AAP) algorithm.

Conclusions UTICalc offers a novel, statistically-satisfactory, UTI-risk-estimate approach in young children.

Commentary Shaikh et al should be congratulated for the strengths of their study. It "mirrors" clinical practice in separating diagnostic process pre-urine sampling (to inform which children are subjected to invasive bladder catheterization) and post urine sampling (to inform antibiotic treatment); it recruited young children in whom UTI is most difficult to

diagnose; it validates the derived model in a separate sample; and they provide evidence it would reduce urine sampling, delayed diagnosis and inappropriate antibiotic use compared with the AAP algorithm. But, is it ready? Here I am torn between academic rigor and the need for pragmatism in clinical practice. Some important issues to consider: (i) it first needs to be externally validated in at least one separate center (and evaluated in a RCT); (ii) its use of routine data means only children in whom clinicians were already suspecting UTI received microbiological confirmation (ascertainment bias); (iii) some untested children will have had a UTI going unrecognized either because they were subsequently managed by another unit or because they were treated with antibiotics serendipitously treating the UTI (ascertainment bias); (iv) clinicians record what they consider clinically and medico-legally important, perpetuating the recording of characteristics already known to be related to UTI[1]; (v) the inclusion of only febrile children prevents an assessment of the diagnostic value of fever (which our study[2] showed not to be useful in primary care); and (vi) the US microbiological definition of UTI includes the presence of leucocytes which inflates the diagnostic value of near patient leucocyte dipstick/microscopy (incorporation bias). However, UTICalc may improve clinical practice. The more pertinent question may be: "Is it superior to the American Academy of Pediatrics recommended algorithm?"—a judgment I feel is best left to my US colleagues.

Alastair D. Hay, MBChB, MD
University of Bristol
Bristol, United Kingdom

References

1. de Salis I, Whiting P, Sterne JAC, Hay AD. Using qualitative research to inform development of a diagnostic algorithm for UTI in children. Fam Pract 2013;30:325-31.
2. Hay AD, Sterne JA, Hood K, Little P, Delaney B, Hollingworth W, et al. Improving the diagnosis and treatment of urinary tract infection in young children in primary care: results from the DUTY Prospective Diagnostic Cohort Study. Ann Fam Med 2016;14:325-36.

Quintupling inhaled fluticasone at first sign of exacerbation

Jackson DJ, Bacharier LB, Mauger DT, Boehmer S, Beigelman A, Chmiel JF, et al. Quintupling Inhaled Glucocorticoids to Prevent Childhood Asthma Exacerbations. *N Engl J Med* 2018;378:891-901.

Question Among children with mild-moderate asthma, what is the therapeutic effect of quintupling maintenance inhaled fluticasone at first sign of exacerbation, compared with no increase, in preventing treatment with systemic corticosteroids?

Design Randomized, controlled, double blind study.

Setting 17 sites across the US.

Participants Children with mild to moderate asthma, 5-11 years of age, who experienced at least one exacerbation treated with systemic corticosteroids.

Intervention Increase from 2 puffs of 44 mcg/puff fluticasone to 220 mcg/puff twice daily at first sign of exacerbation ("yellow zone") versus no increase.

Outcomes Treatment with systemic corticosteroids.

Main Results There was no difference between the treatment groups: relative rate of treatment with systemic corticosteroids, 1.3 (95% CI, 0.8 to 2.1).

Conclusions A 5-times inhaled corticoid steroid increase did not prevent severe exacerbation.

Commentary This study clearly demonstrates that in children aged 5 to 11 with well controlled, mild asthma, who are highly adherent with their inhaled glucocorticoid medication and who start oral prednisolone for an asthma exacerbation triggered by an increase in short-acting beta-2 agonist use, quintupling their maintenance dose of inhaled glucocorticoid has no beneficial effects and can be seen to lead to systemic activity. Unfortunately, adherence with inhaled glucocorticoids is known to be very poor[1] and this study cannot exclude a benefit in patients who have stopped or run out of their maintenance treatment. The criteria for quintupling the dose of inhaled glucocorticoid (yellow zone) was, not unreasonably, based on an increase in short-acting beta agonist (SABA) use: 4 inhalations in 6 hours (2 episodes of 2 puffs) or 6 inhalations in 24 hours or a nighttime awakening requiring SABA. The same criteria were used to signal the need for oral prednisolone but this intervention required more than 6 inhalations in 6 hours, 12 or more inhalations in 24 hours or 2 of 3 consecutive nights with awakenings needing SABA. There was no additional physician assessment or objective measure of lung function. This means the difference between the yellow zone and starting oral prednisolone (the primary outcome) was 2 puffs of SABA in 6 hours, 6 puffs in 24 hours or 2 nights with awakenings rather than 1. As SABA use is common and often used for non-asthma symptoms, this does raise the possibility that some events were not true asthma exacerbations and did not require treatment with prednisolone. Indeed, during the exacerbations, albuterol use peaked at a mean of approximately 3.5 puffs a day, questioning the severity of the exacerbations being prevented. Finally one has to question why a large increase in inhaled glucocorticoid appears to be effective in adolescents and adults[2,3] but is not effective in children. Clearly there is no evidence to support the use of a quintupling dose in children, but perhaps a more "real-life" study with a more objective trigger for starting prednisolone is still required before abandoning self-management plans in children aged 5 to 11 years.

Tim W. Harrison, MBBS, BSc
University of Nottingham
Nottingham, United Kingdom