DEM Journal Club

Article Appraisal

Article: A Prediction Model to Identify Febrile Infants ≤60 Days at Low Risk of Invasive Bacterial Infection
Date of Journal Club: Feb. 18, 2020
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Background and Study Objective(s):

Febrile infants ≤60 days of age are at high risk for serious bacterial infections. Previous criteria to stratify infants as low risk versus moderate or high risk for infection (Boston, Philadelphia, Rochester) use criteria based on expert opinion rather than statistical derivation. More recently, the Step-by-Step approach was developed which is a risk-stratification algorithm that uses age, clinical appearance, urinalysis, procalcitonin, CRP, and ANC to identify infants with invasive bacterial infections (IBI). The authors of this study argue that the older methods of risk stratification are outdated and that procalcitonin results are not readily available in some hospitals to utilize newer methods. The goal of this study was to statistically derive and internally validate a clinical prediction model for IBI in this patient population.

Study Design:

This was a case control study design. Case patients were obtained by retrospective chart review from an electronic database of 11 pediatric emergency departments between July 1, 2011 and June 30, 2016. Ultimately 181 well-appearing, febrile infants ≤60 days old with IBI were included. IBI in this study was defined as culture positive bacteremia or meningitis. Patients were initially included if they had positive blood or CSF cultures that were not thought to be related to contamination. Patients had to be febrile, defined as a rectal temperature ≥38.0°C either on history or in the department. Patients were excluded if they were afebrile, ill-

appearing as per chart documentation, had a complex chronic condition, a non-rectal temperature measurement was obtained, or if clinical appearance was unable to be determined. Each case patient was then matched to two control infants at the same hospital with the closest date of visit to the case patient. The control patients had to meet the same criteria, but have no positive blood or CSF cultures. Controls patients were allowed to be included if they had positive urine cultures.

For both control and case patients data was extracted from the medical record on variables thought to be correlated with IBI. A weighted multiple logistic regression approach was then used for each predictor considered. Each predictor of interest was first considered in the model by itself. Adjusted odds ratios with 95% confidence intervals were used to quantify the magnitude of the association between each predictor and the primary outcome (IBI). Each predictor was then assigned a score on the basis of their adjusted odds ratios. For continuous variables, a cut off value was statistically derived that maximized the area under the curve. The variables selected were then internally validated by using calibration and discrimination metrics.

Results:

Of the 394 infants with IBI who presented to the 11 participating EDs during the 5-year study period, 181 (45.9%) met inclusion criteria as case patients and were matched to 362 control patients. Among the 181 infants with IBI, 155 (85.6%) had bacteremia without meningitis, and 26 (14.4%) had bacterial meningitis.

Four predictors were associated with the presence of IBI: age, highest temperature recorded in the ED, abnormal urinalysis result, and ANC. Using the 4 predictors identified in the final model, an IBI score was developed with a range of possible scores of 0 to 10 points. Among the 492 infants (90.6% of the sample) for whom data were available for each of the predictors (169 case patients and 323 control patients), the sensitivity and specificity of a score $\geq$2 were 98.8% (95% CI: 95.8%–99.9%) and 31.3% (95% CI: 26.3%–36.6%), respectively. All 26 infants with meningitis had scores $\geq$2. Moderate-risk IBI scores of $\geq$3 and $\geq$4 had higher specificity (52.0% and 57.3%, respectively) but lower sensitivity (92.9% and 88.2%, respectively).

Validity of Results:

The study design was appropriate given the rare outcome. The results are plausible as the derived IBI score has a similar sensitivity and specificity to prior similar scores. The trial was multi-centered and based in the ED. In addition, statistically derived cut offs for lab values were obtained rather than relying on expert opinion.

Limitations must be considered. The study excluded “well-appearing” infants although this is not objectively defined and applied retrospectively to a chart review, with no attempt at ascertaining inter-observer reliability. Data collection does not adhere to accepted principles. As per prediction rule methodology, outcome assessors should be blinded to predictor

variables, and vice versa, and this is never confirmed. With only 26 cases of bacterial meningitis, there is potential for model overfit.

Generalizability of Results:

These results are likely generalizable to our patient population as it was a multi-centre study done in pediatric emergency departments. The score uses four predictors including age, highest temperature recorded in the ED, abnormal urinalysis result, and ANC. All of these variables are easily accessible in most ED settings. However, the paper does not disclose who was assessing the patients in the ED (presumably pediatricians) or who was doing the chart review. This may affect the subjective variability among clinicians determining what children are sick versus not sick in order to include them in the score. The score has also only been internally validated, although it is similar to other scores such as the Step-by-Step which has been validated in a different patient population.

The Bottom Line:

The overall approach for this rare illness is reasonable but data collection and analytic standards would greatly benefit from further explanation and adherence to accepted methodology. Despite this the results are clinically sensible. However, this score needs to be validated externally, and the stated sensitivity of 98.8% is unlikely to perform as well in other settings. The exclusion of “well-appearing” patients, especially retrospectively, may be difficult to replicate—and patient appearance can change depending upon time and observer. The score does not improve upon existing scores and was not compared with physician judgment. Finally, the rule does not inform the physician what to do (ie lumbar puncture, antibiotics, admit, etc.); overall these concerns coupled with methodologic issues ensure that this rule is unlikely applicable to a population of our patients.