Critical Review Form
Clinical Prediction or Decision Rule

PGY-4

Kuppermann N, Dayan PS, Levine DA, et al; Febrile Infant Working Group of the Pediatric Emergency Care Applied Research Network (PECARN). A Clinical Prediction Rule to Identify Febrile Infants 60 Days and Younger at Low Risk for Serious Bacterial Infections. JAMA Pediatr. 2019 Apr 1;173(4):342-351.

Objectives: **"to derive and validate an accurate prediction rule in a large, prospectively enrolled, geographically diverse cohort of febrile infants 60 days and younger to identify those at low risk of SBIs [serious bacterial infections]." (p. 343)**

Methods: **This prospective, multicenter, observational study included patients enrolled in a prior study between March 2011 and May 2013. Infants 60 days old and younger with a rectal temperature of 38º C or greater (documented at home, in a prior healthcare center, or in the ED) from whom blood cultures were obtained were eligible for inclusion. Infants who appeared critically ill, had received antibiotics within the previous 48 hours, had a history of prematurity (≤ 36 weeks), had pre-existing medical conditions, had indwelling devices, or had soft-tissue infections were excluded.**

All clinical care was at the discretion of the treating clinicians. ED physicians obtained history and physical exam and performed an assessment of the Yale Observation Scale (YOS) score. They also assigned a clinical suspicion of SBI, prior to lab results coming back, with 5 risk categories: < 1%, 1-5%, 6-10%, 11-50%, or > 50%. SBI was defined as UTI (growth of a single pathogen on urine culture with positive urinalysis), bacterial meningitis (growth of a single pathogen in CSF), or bacteremia (growth of a single non-contaminant pathogen from the blood).

Patients with procalcitonin [PCT] levels were randomly allocated to derivation and validation sets in such a manner as to balance the incidence of bacteremia, bacterial meningitis, and UTIs. Using univariable analysis and binary recursive partitioning analysis, multiple predictors (including PCT) were evaluated to create a decision tree that prioritized sensitivity over specificity for identifying an SBI. The final decision tree chosen was then applied to the validation set.

Out of a total of 1896 febrile infants enrolled, 1821 had a procalcitonin level and underwent a complete assessment for SBI. All patients had blood and urine cultures and 76% had CSF cultures obtained. There were 908 patients assigned to the derivation set and 913 assigned to the validation set. For those patients without CSF obtained, follow-up (by inpatient observation, telephone, or medical record review), none were later found to have bacterial meningitis.

Guide		Comments
I.	***Is this a newly derived instrument* (Level IV)?**	
A.	Was validation restricted to the retrospective use of statistical techniques on the original database? (If so, this is a Level IV rule & is not ready for clinical application).	No. Validation occurred retrospectively on a separate cohort of patients selected from the same database as the derivation cohort.
II.	**Has the instrument been validated? (Level II or III). If so, consider the following:**	
1a	Were all important predictors included in the derivation process?	Yes. The predictor variables assessed included age group (≤ 28 days vs > 28 days), temperature, duration of fever, YOS score, clinical suspicion, urinalysis, WBC count, absolute neutrophil count (ANC), and serum procalcitonin level.
1b	Were all important predictors present in significant proportion of the study population?	Yes. Just over 30% of patients were ≤ 28 days of age, a broad range of clinical suspicions was present (though only 1.3% had a > 50% predicted risk of SBI), patients had a reasonably wide range in terms of duration of fever (though the majority had a fever for < 12 hours), and there appears to be wide range of YOS scores.
1c	Does the rule make clinical sense?	Yes. The final clinical rule to identify infants at low risk of SBI was as follows: 1. Negative urinalysis 2. ANC of 4000/µL or lower 3. Serum PCT 0.5 ng/mL or lower. ANC and PCT have previously been shown to independently predict SBIs in infants (Hamiel 2018) and urinalysis results would be a helpful addition to exclude a urinary tract infection. It seems unusual that clinical suspicion was not an independent predictor of SBI, but this may be due in part to the exclusion of infants who appeared critically ill.
2	Did validation include prospective studies on several different populations from that used to derive it (II) or was it restricted to a single population (III)?	No. Although validation occurred in a database including from 22 different pediatric EDs in the US, this was only performed in a retrospective fashion. No prospective validation has occurred. Additionally, validation occurred in a patient population that was essentially identical to the derivation cohort.
3	*How well did the validation study meet the following criteria?*	

3a	Did the patients represent a wide spectrum of severity of disease?	No. As noted above, a broad range of clinical suspicions was present (though only 1.3% had a > 50% predicted risk of SBI) and there appears to be wide range of YOS scores. However, patients who appeared critically ill were excluded from the study, hence limiting this to a relatively less ill patient population.
3b	Was there a blinded assessment of the gold standard?	There is no true, singe gold standard for the diagnosis of SBI. For the purposes of this study, SBI was defined by bacterial growth in urine, blood, or CSF, which seems like a reasonable "gold standard." There is no mention of blinding outcome assessors to clinical and laboratory data, but given that culture results are quite objective, this is not likely to introduce significant bias.
3c	Was there an explicit and accurate interpretation of the predictor variables & the actual rule without knowledge of the outcome?	Yes. This was a retrospective study using prospectively collected data; subjective variables (such as clinical suspicion) were documented prior to culture results being available, and lab results (e.g. PCT and ANC) would similar result prior to culture results being available. It therefore does not seem possible for the outcomes to have affected the interpretation of the predictor variables.
3d	Did the results of the assessment of the variables or of the rule influence the decision to perform the gold standard?	Yes. The "gold standard" in this case involved growth of bacteria from urine, CSF, or blood. While all patients enrolled had blood and urine cultures sent, not all patients had a CSF culture, and it is likely that some of the variables influenced the decision to perform a lumbar puncture.
4	How powerful is the rule (in terms of sensitivity & specificity; likelihood ratios; proportions with alternative outcomes; or relative risks or absolute outcome rates)?	In the derivation cohort, the rule performed as follows: • Sensitivity 98.8% (95% CI 92.5-99.9) • Specificity 63.1% (95% CI 59.7-66.4) • LR- 0.02 (95% CI 0.003-0.14) • LR+ 2.68 (95% CI 2.44-2.93) In the validation cohort, the rule performed as follows: • Sensitivity 97.7% (95% CI 91.3-99.6) • Specificity 60.0% (95% CI 56.6-63.3) • LR- 0.04 (95% CI 0.01-0.15) • LR+ 2.44 (95% CI 2.23-2.67)
III.	**Has an impact analysis demonstrated change in clinical behavior or patient outcomes as a result of using the instrument? (Level I). If so, consider the following:**	

1	How well did the study guard against bias in terms of differences at the start (concealed randomization, adjustment in analysis) or as the study proceeded (blinding, co-intervention, loss to follow-up)?	N/A. No impact analysis was performed.
2	What was the impact on clinician behavior and patient-important outcomes?	N/A.

Limitations:

1. **A convenience sample of patients was enrolled and no information was provided regarding patients who were eligible but not enrolled.**

2. **Patients who appeared critically ill were excluded, resulting in a lower risk patient population (spectrum bias); this is likely okay as it should result in a cohort of patients for whom clinical uncertainty existed.**

3. **While the rule was validated in a separate group of patients from the derivation cohort, this cohort was in many ways identical to the derivation cohort; in fact, the authors took the entire cohort and split them in a manner that balanced the groups with respect to bacteremia, bacterial meningitis, and UTIs. Further research should seek to validate these results in a truly novel cohort of patients.**

4. **A significant proportion of patients (24%) did not undergo a lumbar puncture and hence did not have CSF culture results available.**

Bottom Line:

This retrospective analysis of prospectively collected data sought to derive and validate a clinical decision rule using PCT for the evaluation of febrile infants (60 days old and younger) for SBI. The final rule (negative urinalysis, ANC of 4000/µL or lower, and serum PCT 0.5 ng/mL or lower) had useful negative likelihood ratios in both the derivation and validation sets (0.02 and 0.04, respectively). Given the manner in which the cohorts were obtained, these results should be validated in a more unique cohort of patients before this rule is employed.