PGY-3

Critical Review Form
Clinical Prediction or Decision Rule

Gomez B, Mintegi S, Bressan S, Da Dalt L, Gervaix A, Lacroix L; European Group for Validation of the Step-by-Step Approach. Validation of the "Step-by-Step" Approach in the Management of Young Febrile Infants. Pediatrics. 2016 Aug;138(2).

Objectives: **"The "Step by Step" is a new algorithm developed by a European group of pediatric emergency physicians. Its primary objective was to identify a low risk group of infants who could be safely managed as outpatients without lumbar puncture nor empirical antibiotic treatment…The objective of this study was to prospectively validate these results in a larger multicenter population." (p. 2)**

Methods: **This multicenter, prospective validation study was conducted at 11 pediatric emergency departments (8 in Spain, 2 in Italy, 1 in Switzerland) between September 2012 and August 2014. Patients aged 90 days or less presenting with a fever of 38ºC or higher were eligible for enrollment. Patients with a clear source of infection, those with only subjective fever (not confirmed by thermometer either at home or in the ED), and those without 1 or more of the mandatory tests performed were excluded. Mandatory testing consisted of a urine dipstick and culture collected by aseptic technique, white blood cell count (WBC), CRP, procalcitonin (PCT), and a blood culture. Further testing, antibiotic administration, and disposition were at the discretion of the treating physician.**

Following data collection, the Step-by-Step approach, Rochester criteria, and Lab-score were applied to patients and the diagnostic performances of the 3 sets of criteria were compared. For patients who were discharged, parents or caregivers were contacted within one month of the initial ED visit; if they could not be reached after 3 attempts, the electronic registries of the ED and Public Health System were checked for additional primary care or hospital visits. Invasive bacterial infection (IBI) was defined as isolation of a non-contaminant organism from CSF or blood. A non-IBI was defined as a urinary tract infection with a positive urine culture, bacterial gastroenteritis (with a positive stool culture), or a diagnosis highly suggestive of a bacterial infection with no positive culture in whom the principal investigators determined this to be the most appropriate classification.

Among 2635 infants 90 days old or younger with fever without a clear source of infection, 2185 were included in the study. The median age was 47 days and 59./5% were male. There were 504 included patients diagnosed with a bacterial infection (23.1%), including 87 (3.9%) with an IBI and 417 (19.1%) with a non-IBI.

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. This is a prospective validation of a CDR that was previously evaluated respectively (Mintegi 2014), conducted in 11 pediatric emergency departments.
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?	N/A. This was not a derivation study. This step-by-step approach was not statistically derived but was presumably determined by consensus.
1b	Were all important predictors present in significant proportion of the study population?	N/A. This was not a derivation study.
1c	Does the rule make clinical sense?	Mostly yes. The clinical rule is a step-by-step decision aid that includes several relevant clinical features, including ill-appearance, age 21 days or less, and presence of white blood cells in the urine. The study then goes on to use elevated lab values, such as procalcitonin, CRP, and absolute neutrophil count to classify patients into risk categories. While the use of biomarkers such as PCT and CRP in evaluation of the febrile infant is somewhat novel, there are studies demonstrating a higher risk of IBI in patients with elevations in these biomarkers (Bressan 2012, England 2014).
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)?	Yes. This study is a multicenter trial conducted at 11 pediatric EDs in 3 different countries. Given that these are pediatric EDs it is likely that they were all tertiary care facilities rather than community EDs staffed by non-pediatric emergency physicians, and these results should be validated in this specific setting (external validity).
3	*How well did the validation study meet the following criteria?*	
3a	Did the patients represent a wide spectrum of severity of disease?	Yes. There appears to be a wide range of illness severity, with nearly 20% diagnosed with a non-IBI, 4% with an IBI, and another 4.5% with a possible bacterial infection. The majority of patients (>71%) did not have a bacterial infection diagnosed. Half of patients were deemed ill enough to require antibiotics and nearly 60% were admitted to the hospital (1.6%

		to an ICU). The majority of patients (87.7%) were classified as "well appearing."
3b	Was there a blinded assessment of the gold standard?	No. The authors do not specifically mention blinding to the predictor variables when classifying patients by outcome, but for the vast majority of patients, final diagnosis was assigned based on the presence of absence of bacteria on culture results, which is entirely objective. Among patients diagnosed with a "possible bacterial infection" (4.5%) and among some patients with a non-IBI, there could be some subjectivity, and lack of blinding to predictors and decision rule results could have biased the reported outcomes.
3c	Was there an explicit and accurate interpretation of the predictor variables & the actual rule without knowledge of the outcome?	Yes. Predictor variables were documented prospectively, with no knowledge of culture results (which were used to make the final diagnosis in the vast majority of patients).
3d	Did the results of the assessment of the variables or of the rule influence the decision to perform the gold standard?	Likely yes. The gold standard in this case is represented by blood, urine, and CSF cultures. It is likely that in many cases the decision to obtain such cultures (or perform a lumbar puncture) was made in part based on the result of clinical and laboratory assessment (verification bias).
4	How powerful is the rule (in terms of sensitivity & specificity; likelihood ratios; proportions with alternative outcomes; or relative risks or absolute outcome rates)?	For identifying IBIs, the Step by Step approach had better sensitivity and negative likelihood ratio than the Rochester criteria and Lab-score, but a poorer specificity and positive likelihood ratio than the Lab-score. • Step by Step ○ Sensitivity 92.0% (95% CI 84.3-96.0) ○ Specificity: 46.9% (95% CI 44.8-49.0) ○ LR+ 1.73 (95% CI 1.61-1.85) ○ LR- 0.17 (0.08-0.35)
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 has been performed.

2	What was the impact on clinician behavior and patient-important outcomes?	N/A.

Limitations:

1. **All of the study sites involved were pediatric EDs. The Step by Step approach ha not been validated for use by non-pediatric emergency physicians in community settings (external validity).**

2. **There is no mention of blinding outcome assessors to the results of the clinical decision rules or their components.**

3. **Not all patients underwent the same testing (i.e. blood cultures and lumbar puncture). While this makes sense given the nature of the decision rule, it is likely that in many cases the decision to obtain such cultures (or perform a lumbar puncture) was made in part based on the result of clinical and laboratory assessment (verification bias).**

4. **No impact analysis has yet been performed to determine whether this approach would reduce testing without an increase in adverse outcomes.**

Bottom Line:

This prospective, multicenter study found that the Step by Step approach was associated with a better sensitivity and negative likelihood ratio than the Rochester criteria or Lab-score for diagnosing an invasive bacterial infection among febrile infants (90 days old or less) presenting to a pediatric ED. The negative LR associated with this approach (0.17) would result in a moderate decrease in disease probably when negative, but in higher risk patients may be insufficient to properly rule out an IBI. One of the biggest limitations seems to be the use of 21 days as a cutoff at one step, as 4 of the 7 "low risk" patients found to have an IBI were 22-28 days of age.