Critical Review Form
Diagnostic Test

Milcent K, Faesch S, Gras-Le Guen C, et al. Use of Procalcitonin Assays to Predict Serious Bacterial Infection in Young Febrile Infants. JAMA Pediatr. 2016 Jan;170(1):62-9.

Objectives: **"to assess the diagnostic accuracy of PCT [procalcitonin] assays and to compare it with other, routinely used biomarkers for detecting SBI [serious bacterial infection] and IBI [invasive bacterial infection] in febrile infants aged 7 to 91 days and for sub-groups of infants according to their age (7-30 days or >30 days) and the duration of fever (≤6 hours)." (p. 63)**

Methods: **This prospective, multicenter, cohort study was conducted in 15 French pediatric EDs between October 1, 2008 and March 31, 2011. Infants between 7 and 91 days old with a temperature of 38 ºC or higher (at home or in the ED) were eligible for inclusion. Patients receiving antibiotics within the previous 48 hours and those with "major comorbidities" (immune deficiency, congenital abnormality, or chronic disease) were excluded.**

After clinical evaluation and prior to test results coming back, treating physicians classified patients as well-appearing, minimally ill, moderately ill, or very ill. Testing was performed at the discretion of treating clinicians, although all patients had a PCT level checked. Definite SBI was defined by isolation of a bacterial pathogen from cultures of blood, CSF, stool, or urine, and patients with possible (but not definitive) SBI were considered as not having definite SBI for diagnostic test performance analysis. IBI was defined as bacteremia or bacterial meningitis.

Out of 2981 eligible infants, 2273 were enrolled. An additional 226 patients were excluded, leaving 2047 in the final analysis. Nearly 60% of patients were male and 73.5% were admitted to the hospital. The prevalence of a definite SBI was 6.8%. Of 115 patients with a definite SBI, 115 were diagnosed with a UTI, 13 with bacteremia, and 8 with meningitis.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did clinicians face diagnostic uncertainty?**	Yes. This study enrolled infants between 7 and 91 days of age with fever, regardless of clinical appearance. While the possibility of a SBI is always a concern among this patient population, a large number of these patients have viral illnesses or other, nonbacterial, causes of fever. Extensive testing is often performed, particularly in those < 30 days of age, including blood cultures,

		urinalysis, and lumbar puncture. Use of a simple blood test, such as PCT, to aid in the diagnosis of SBI has the potential to be very helpful.
B.	**Was there a blind comparison with an independent gold standard applied similarly to all patients? (Confirmation Bias)**	No. Unfortunately, there is no gold standard for the diagnosis of pediatric SBI. Test comparisons were made with blinding to PCT results: "The attending physician made the diagnosis, categorized as SBI or no bacterial infection, masked to the PCT value." (p.63) Additionally, "All cases of IBI were reviewed by 2 pediatric infectious disease specialists and 2 bacteriologists, all masked to the PCT results." (p. 63) However, testing was NOT applied similarly to all patients: blood cultures were performed in 61.5% of patients, urine culture in 67.3%, lumbar puncture in 64.8%, and chest radiography in 64.5% (partial verification bias).
C.	**Did the results of the test being evaluated influence the decision to perform the gold standard? (Ascertainment Bias)**	No. While there is no true gold standard, all testing (including blood cultures, urinalysis, and lumbar puncture) was performed at the discretion of the treating physician without knowledge of the results of PCT testing.
II.	**What are the results?**	

A.	**What likelihood ratios were associated with the range of possible test results?**	• The AUC for PCT was 0.81 for diagnosis of SBI and 0.91 for IBI; the optimal cutoff was determined to be 0.3 ng/mL.
		• Using a cutoff of 0.3, PCT had the following test characteristics for diagnosis of definite SBI:
		  ○ Sensitivity 74% (95% CI 62 to 84)
		  ○ Specificity 78% (95% CI 75 to 80)
		  ○ LR+ 3.3 (95% CI 2.8 to 3.9)
		  ○ LR- 0.3 (95% CI 0.2 to 0.5)
		• Using a cutoff of 0.3, PCT had the following test characteristics for diagnosis of IBI:
		  ○ Sensitivity 90% (95% CI 68 to 99)
		  ○ Specificity 78% (95% CI 75 to 80)
		  ○ LR+ 4.0 (95% CI 3.3 to 4.8)
		  ○ LR- 0.1 (95% CI 0.03 to 0.4)

III.	**How can I apply the results to patient care?**	
A.	**Will the reproducibility of the test result and its interpretation be satisfactory in my clinical setting?**	Yes. This is a routine blood test that would be easily performed in most institutions and should be reproducible assuming the same assay is used.
B.	**Are the results applicable to the patients in my practice?**	Yes. Febrile infants are seen routinely at Children's Hospital (and most community EDs) and their evaluation should be similar to patients enrolled in this study.

C.	**Will the results change my management strategy?**	No. This study demonstrates poor to moderate likelihood ratios associated with PCT in the diagnosis of SBI (LR+ 3.3 and LR- 0.3), suggesting little change in the probability of disease with either a positive or negative test. For IBI, the LR- was 0.1, which would result in a significant decrease in the probability of disease. While patients with a negative PCT would still need testing for SBI, this could potentially obviate the need for blood cultures and lumbar puncture (since these defined IBI). However, as this study did not look at test characteristics for PCT among patients < 30 days of age (i.e. those who would be more likely to have blood cultures and lumbar puncture) it is unclear if similar test characteristics would be found in this patient population. Further testing in this subset of patients will be needed be necessary before such a change in practice can be made.
D.	**Will patients be better off as a result of the test?**	No. In isolation, PCT performed poorly in terms of both ruling in and ruling out SBI and IBI. It is possible that PCT, when used in conjunction with other findings as part of a clinical decision rule, may be helpful in the evaluation of febrile infants, but until such rules are derived and validated, PCT alone should not be used for this purpose.

Limitations:

1. **Though not specifically mentioned, this appears to be a convenience sample of patients, as the authors mention that several eligible patients were not included. No description of these patients was provided.**

2. **The authors chose a rather heterogenous patient population for their study; patients 7-28 days old are at much higher risk of SBI and IBI, and PCT may perform differently in this patient population (spectrum bias).**

3. **The "gold standard" for diagnosis of SBI and IBI included culture results from blood, urine, and CSF, but these were not obtained on all patients (partial verification bias).**

4. **Patients with possible, but not definitive, SBI were classified as NOT having SBI. This would potentially underestimate the prevalence of SBI and potentially impact the test characteristics calculated.**

Bottom Line:

This prospective cohort study involving febrile patients aged 8 to 90 days found that PCT (using a cutoff of 0.3 ng/mL) had a LR+ of 3.3 and LR- 0f 0.3 for diagnosis of a SBI, suggesting little utility in isolation. For the diagnosis of an IBI (bacteremia or meningitis), PCT had a potentially clinically useful LR- of 0.1, suggesting it may be possible to forego blood cultures and a lumbar puncture in patients with a negative PCT. Unfortunately, this study did not look at PCT test characteristics specifically in patients < 28 days of age, and this finding may not hold in the particular subset of patients at highest risk for IBI.