Critical Review Form
Meta-analysis

PGY-1

Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. Lancet Infect Dis. 2013 May;13(5):426-35.

Objectives: **"to investigate the ability of procalcitonin to differentiate between sepsis and systemic inflammatory response syndromes [SIRS] of non-infectious origin in critically ill patients." (pp. 426-427)**

Methods: **A systematic search of Medline, Embase, ISI Web of Knowledge, the Cochrane Library, Scopus, BioMed Central, and Science Direct was conducted from inception to February 21, 2012, limited to English, German, or French. Studies assessing the diagnostic accuracy of procalcitonin in the diagnosis of sepsis were evaluated for inclusion. Inclusion required that studies assess the accuracy of procalcitonin in differentiating sepsis from SIRS of non-infectious etiology in critically ill patients. Studies were required to have a well-defined reference standard for sepsis, to include definitions established by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference, or the German Sepsis Society. The presence of infection had to be microbiologically confirmed, or at least suspected due to the presence of white blood cells in a normally sterile fluid, a perforated viscus, radiographic findings of pneumonia associated with purulent sputum production, or a syndrome associated with a high risk of infection.**

Two investigators abstracted data independently, including methodological characteristics, study population characteristics, setting, severity of illness, procalcitonin assay and cutoff used, and the number of true and false positives and negatives in each study. Study quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) checklist.

Out of 136 articles selected for full-text review, 30 studies were selected for inclusion. One of the studies selected comprised 2 datasets (medical and surgical), therefore 31 total datasets were included. A total of 3244 critically ill patients were included in the analysis, of whom 1863 (57%) had sepsis, and 1381 (43%) were deemed to have SIRS without infection. The prevalence of sepsis ranged from 34% to 88% among the studies. Four studies assessed pediatric patients, while the remaining 27 datasets assessed adults. 17 studies were conducted solely in the ICU; two studies were conducted solely in the emergency department (ED), while an additional two were conducted using a combination of ED and inpatient subjects. The procalcitonin cut-off varied widely between studies, ranging from 0.1 to 15.75 ng/mL (median 1.1, IQR 0.5 to 2.0).

Guide	Question	Comments
I	***Are the results valid?***	
1.	Did the review explicitly address a sensible question?	Yes. Early identification of sepsis is important, in part because early delivery of antibiotics has been shown to decrease mortality (Gaieski 2010). Differentiating patients with SIRS of noninfectious etiology from those with sepsis can be difficult, and reliance on source testing and culture results can lead to both delays in diagnosis and false negative results (Bates 1997). Serum biomarkers (including procalcitonin, c-reactive protein, and interleukin-6) may aid in the diagnosis of sepsis and lead to earlier and more appropriate antibiotic utilization (Ventetuolo 2008).
2.	Was the search for relevant studies details and exhaustive?	Yes. The authors searched all of the major medical databases, including Medline, Embase, ISI Web of Knowledge, the Cochrane Library, Scopus, BioMed Central, and Science Direct. They included studies in English, French, and German. While they did not review society conference abstracts, registered clinical trials, or the gray literature, they still likely missed few relevant trials.
3.	Were the primary studies of high methodological quality?	No. "Overall, the methodological quality was moderate. None of the studies fulfilled all of the items, but all studies fulfilled at least four items. 22 studies (73%) met at least 50% of the items. Items 3 (reference standard), 5 (partial verification bias), 6 (differential verification bias), and 14 (withdrawals) were fulfilled by all studies. Reports of test review bias (item 10) and uninterpretable results (item 13) were poor (appendix)." (p.430)
4.	Were the assessments of the included studies reproducible?	Yes and no. The authors used the (QUADAS) checklist to assess the methodology of the included studies, a well-validated tool. However, the inter-rater reliability for the assessment of the quality items was only moderate (kappa = 0.59).
II.	***What are the results?***	
1.	What are the overall results of the study?	The pooled estimate of sensitivity was 0.77 (95% CI 0.72-0.81); specificity was 0.79 (95% CI 0.74-0.84); and the area under the ROC curve was 0.85 (95% CI 0.81-0.88). The resulting positive likelihood ratio (LR) is 3.7, and negative LR is 0.29.
2.	How precise are the results?	See above.

3.	Were the results similar from study to study?	No. There was substantial heterogeneity noted, with I^2 values of 77.81% for sensitivity and 78.06% for specificity.
III.	***Will the results help me in caring for my patients?***	
1.	How can I best interpret the results to apply them to the care of my patients?	Uncertain. The reported pooled sensitivity and specificity from the meta-analysis correspond to positive and negative likelihood ratios of 3.7 and 0.29, which will only result in small changes in disease probability. Therefore, caution will need to be exercised when interpreting test results. Interval likelihood ratios may provide more clinically useful information, but were not provided. The authors suggest that while procalcitonin alone cannot differentiate noninfectious SIRS from sepsis, it can be used in conjunction with additional clinical information to aid in diagnosis and management. Unfortunately, the authors offer no prescription for how this information can be usefully included in decision-making. No clinical decision/prediction rules including procalcitonin levels have been developed to help differentiate sepsis from non-infectious SIRS. If procalcitonin is to become a relevant aspect of sepsis care, additional research will need to identify a particular clinical role with an improvement in patient-oriented outcomes.
2.	Were all patient important outcomes considered?	No. The potential impact of procalcitonin measurement on clinical decision-making, and any resultant effect on mortality, length of stay, or other important morbidities was beyond the scope of the meta-analysis.
3.	Are the benefits worth the costs and potential risks?	Uncertain. There is very little risk associated with obtaining a procalcitonin level. Cost is the main concern, but is likely low relative to the overall healthcare cost associated with sepsis and SIRS. There currently appears to be little, if any, benefit to checking a level, as it is unclear how to interpret the results in the context of the overall clinical picture.

Limitations:

1. **There was substantial heterogeneity among the included studies, which differed widely with respect to location, disease severity, and procalcitonin cutoff value (range 0.1 to 15.75 ng/ml). The resulting meta-analysis is of little value given this heterogeneity.**

2. **While inclusion required infection to be microbiologically confirmed or clinically suspected, there was little information as to how infection was proved in most of the studies.**

3. **Given the high rate of culture-negative sepsis previously reported (Phua 2013), inclusion of studies using culture alone as the gold standard could potentially lead to an increased false-positive rate for procalcitonin, decreasing the perceived specificity.**

4. **The majority of studies recruited patients from ICUs, while only four studies included patients recruited from the emergency department (external validity).**

5. **Significant publication bias was detected: studies with less desirable results appeared less likely to be published, potentially inflating the diagnostic accuracy of the test in the meta-analysis.**

Bottom Line:

The reported pooled sensitivity and specificity from the meta-analysis correspond to positive and negative likelihood ratios of 3.7 and 0.29, which will only result in small changes in disease probability. Therefore, caution will need to be exercised when interpreting test results. Interval likelihood ratios may provide more clinically useful information, but were not provided. If procalcitonin is to become a relevant aspect of sepsis care, additional research will need to identify a particular clinical role with an improvement in patient-oriented outcomes.