Critical Review Form
Diagnostic Test

PGY-3

Discriminative value of inflammatory biomarkers for suspected sepsis. J Emerg Med. 2012 Jul;43(1):97-106.

Objectives: **"To characterize the relationships between PCT [procalcitonin], interleukin-6 (IL-6), C-reactive protein (CRP), and several clinically relevant outcomes including the following: infection likelihood, sepsis, severity, septicemia, and clinical outcomes including length of stay (LOS) and discharge to a higher level of care." (p. 98)**

Methods: **This retrospective study was performed on patients from two cohorts: the Community Acquired Pneumonia & Sepsis Outcome Diagnostics study (CAPSOD) and the Duke Febrile Illness Cohort (DFIC). Subjects were enrolled at the Duke University Medical Center emergency department (ED) and the Durham VA Medical Center ED from July 2003 to December 2003 and from December 2006 to December 2007. Patients with known or suspected infection meeting two or more SIRS criteria were flagged for eligibility by ED providers during daytime hours only. Exclusion criteria were age < 18 years, an imminently terminal comorbid condition, HIV/AIDS with a CD4 count < 50 cells/mL, or treatment with antibiotics for an unrelated condition.**

Study coordinators reviewed and abstracted data obtained during the ED encounter. Patients were also assessed for 30-day outcomes, including mortality, hospital LOS, admission to an ICU, ICU LOS, in-hospital mortality, and discharge disposition. Blood and serum samples were frozen following collection and later thawed and analyzed for PCT, IL-6, and CRP.

One of two physicians, blinded to biomarker results, reviewed study data and the medical record and assigned a likelihood of infection based on the following categories:

Category 1: definite infection with an identified etiologic agent.
Category 2: definite infection without an identified etiologic agent.
Category 3: infection neither confirmed nor excluded.
Category 4: no evidence of infection.

An independent assessment of 10% of the patient records revealed a high inter-rater reliability for infection (kappa = 0.82). The likelihood of infection was then dichotomized into those with "infection present" (defined as category 1, 2, or 3) or "infection absent" (category 4). Sepsis was defined as SIRS with evidence of infection but without hypotension, hypoperfusion, or organ failure. Severe sepsis was

defined as sepsis with evidence of end-organ damage (lactate > 1.5X the upper limit of normal, pH < 7.30, platelet count < 80,000/hpf, need for intubation, paO2/FiO2 < 250, or urine output < 0.5 mL/kg/h despite adequate fluid resuscitation). Septic shock was defined as sepsis with either SBP < 90 mmHg or MAP < 65 mmHg despite fluid challenge, or a blood lactate ≥ 4 mmol/L. Discharge to a higher level of care consisted of any of the following: discharge to a skilled nursing facility, hospice enrollment, death within 28 days, or ongoing hospitalization at 28 days.

A total of 336 patients with suspected sepsis were enrolled. The mean age was 52 years and 51.5% were male. Of these, 89 (26.5%) were deemed to have non-infectious etiologies (Category 4). Of the remaining 247 subjects, 202 (81.8%) had uncomplicated sepsis, 28 (11.3%) had severe sepsis, and 17 (6.9%) had septic shock. Blood cultures were positive in 55 of 259 (21.2%) subjects.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did clinicians face diagnostic uncertainty?**	Mostly yes. This was a cohort of patients with 2 or more SIRS criteria and "known or suspected infection." (p. 98) In many of these cases, it is likely that infection was suspected but not confirmed, with the ultimate diagnosis not made until later during hospitalization. The decision to start antibiotics in patients with SIRS but without confirmed infection can be a difficult one. Delays in antibiotic administration has been linked to increased mortality in septic patients, while unnecessary administration of antibiotics to patients with infection increases the risks of adverse reactions and C. diff infection, and potentially increases antibiotic resistance.
B.	**Was there a blind comparison with an independent gold standard applied similarly to the treatment group and to the control group? (Confirmation Bias)**	Yes. There was no treatment/control group, but all patient charts were independently assessed by two physicians who were blinded to biomarker results. Patients were assigned to one of 4 categories regarding infectious status, as previously discussed.
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" for sepsis, all patient charts were reviewed regardless of the results of biomarker testing.
II.	**What are the results?**	
A.	**What likelihood ratios were associated with**	For the differentiation of sepsis from SIRS without infection, CRP demonstrated the hightest diagnostic accuracy, with an

<table>
<tr><td></td><td>the range of possible test results?</td><td>AUC of 0.75, compared to PCT and IL-6 (AUC 0.72 and 0.69 respectively).

PCT greater than 3 ng/mL demonstrated a LR+ of 6.3, while a level less than 0.1 ng/mL demonstrated a LR- of 0.51

Table 1. Test characteristics for the diagnosis of infection
<table>
<tr><th>Test</th><th>Cutoff</th><th>Sensitivity</th><th>Specificity</th><th>LR+</th><th>LR-</th></tr>
<tr><td rowspan="3">PCT (ng/mL)</td><td>0.1</td><td>67.9</td><td>63.4</td><td>1.9</td><td>0.51</td></tr>
<tr><td>0.5</td><td>40.7</td><td>87.2</td><td>3.2</td><td>0.68</td></tr>
<tr><td>3</td><td>18.4</td><td>97.1</td><td>6.3</td><td>0.84</td></tr>
<tr><td rowspan="3">IL-6 (pg/mL)</td><td>40</td><td>58.4</td><td>67.4</td><td>1.8</td><td>0.62</td></tr>
<tr><td>100</td><td>43.2</td><td>80.3</td><td>2.2</td><td>0.71</td></tr>
<tr><td>500</td><td>14.1</td><td>96.2</td><td>3.7</td><td>0.89</td></tr>
<tr><td rowspan="3">CRP (mg/dL)</td><td>7</td><td>90.4</td><td>32.7</td><td>1.3</td><td>0.29</td></tr>
<tr><td>40</td><td>67.6</td><td>68.4</td><td>2.1</td><td>0.47</td></tr>
<tr><td>100</td><td>43.1</td><td>87.9</td><td>3.6</td><td>0.65</td></tr>
</table>
For the differentiation of those with and without septicemia, PCT demonstrated the highest accuracy, with an AUC of 0.79. The AUCs for IL-6 and CRP were 0.70 and 0.67 respectively.

Table 2. Test characteristics for the diagnosis of septicemia
<table>
<tr><th>Test</th><th>Cutoff</th><th>Sensitivity</th><th>Specificity</th><th>LR+</th><th>LR-</th></tr>
<tr><td rowspan="3">PCT (ng/mL)</td><td>0.1</td><td>90.8</td><td>37.5</td><td>1.5</td><td>0.25</td></tr>
<tr><td>0.5</td><td>72.6</td><td>69.5</td><td>2.4</td><td>0.39</td></tr>
<tr><td>3</td><td>47.2</td><td>89.9</td><td>4.7</td><td>0.59</td></tr>
<tr><td rowspan="3">IL-6 (pg/mL)</td><td>40</td><td>90.2</td><td>33.9</td><td>1.4</td><td>0.29</td></tr>
<tr><td>100</td><td>68</td><td>62.0</td><td>1.8</td><td>0.52</td></tr>
<tr><td>500</td><td>27</td><td>89.4</td><td>2.5</td><td>0.82</td></tr>
<tr><td rowspan="3">CRP (mg/dL)</td><td>7</td><td>82.3</td><td>38.7</td><td>1.3</td><td>0.46</td></tr>
<tr><td>40</td><td>60.1</td><td>65.6</td><td>1.7</td><td>0.61</td></tr>
<tr><td>100</td><td>30.7</td><td>88.1</td><td>2.6</td><td>0.79</td></tr>
</table></td></tr>
<tr><td>III.</td><td>How can I apply the results to patient care?</td><td></td></tr>
<tr><td>A.</td><td>Will the reproducibility of the test result and its interpretation be satisfactory in my clinical setting?</td><td>Yes. These are laboratory tests that are easily reproduced. It is important to note that different assays will result in different values for the same lab test, and this will need to be taken into account.</td></tr>
<tr><td>B.</td><td>Are the results applicable to the patients in my practice?</td><td>Yes. We are often faced with the dilemma of differentiating septic from non-septic, clinically unstable, patients. This is often difficult, and a lab test to help make this differentiation would be invaluable in helping to direct treatment and work-</td></tr>
</table>

		up.
C.	**Will the results change my management strategy?**	No. The diagnostic test characteristics for these 3 lab values were poor. A PCT > 3 is most promising (LR+ 6.3) and could potentially alter management, though how often such a value would be obtained in patients not already being treated for sepsis is uncertain. These tests, in isolation, cannot be used to differentiate sepsis from non-infectious SIRS. Clinical decision rules utilizing these tests have not yet been developed or validated, making their use as part of a broader clinical picture difficult to envision.
D.	**Will patients be better off as a result of the test?**	No. As these tests do not help differentiate sepsis from non-infectious SIRS, they cannot be used to make decisions regarding treatment or further work-up.

Limitations:

1. **Means of assessing 30-day outcomes not clearly defined.**

2. **This was a cohort of all potentially septic patients, rather than only including those in whom the diagnosis was uncertain (spectrum bias). This tends to result in an overestimate of sensitivity and specificity.**

3. **No 95% confidence intervals were provided for diagnostic test characteristics, nor could they be calculated given the information provided.**

4. **The study utilized a convenience sample of patients enrolled during daytime hours only. This could potentially limit the external validity of the study.**

5. **Patients with infection "neither confirmed nor excluded" were considered to have an infection. This would potentially deflate the sensitivity and inflate the specificity. A sensitivity analysis was not performed with these patients in the "no infection" group.**

Bottom Line

This study of ED patients with 2 or more SIRS criteria with possible infection assessed the diagnostic accuracy of PCT, IL-6, and CRP in the diagnosis of sepsis. The tests all performed poorly, with likelihood ratios that would not result in significant changes to the probability of disease. The one exception is a PCT of 3 or more, which had a LR+ of 6.3, which could potentially lead to the administration of antibiotics in patients with a positive test. It is unclear, however, how often such a patient would not already be treated for sepsis. Routinely checking biomarkers in cases of suspected sepsis does not seem clinically useful in differentiating those with sepsis from those with non-infectious SIRS.