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Washington University Emergency Medicine Journal Club
Biomarkers (e.g. Procalcitonin) to Diagnose Sepsis in the ED

Vignette

You are rotating at a hospital just outside of Honolulu, HI. A patient presents from dialysis with nausea and vomiting. The patient has been feeling unwell for several days, presented to dialysis and had several episodes of non-bloody emesis. Their dialysis session was completed and then the patient was transferred to the ED for further evaluation. The patient denies abdominal pain and respiratory symptoms. The patient is afebrile, tachycardic with a heart rate in the 120s, a blood pressure of 95/65, mildly tachypneic with a respiratory rate of 22, saturating 98% on room air. On exam, the patient appears to have dry mucous membranes, clear lungs, soft abdomen. The patient has an in-dwelling right IJ dialysis catheter; the site is appropriately dressed, appears clean and dry and has no surrounding erythema.

Basic work-up is started and the patient has a clear chest X-ray, mild leukocytosis of 13,000, EKG showing sinus tachycardia. Creatinine is elevated to 5, other electrolytes are within normal limits. Point of care lactate is mildly elevated at 2.5. After a small bolus of IV fluids, the patient remains tachycardic with a soft blood pressure. You consider the possibility that the patient may be septic and consider the initiation of broad spectrum antibiotics.

Since your medical license hasn't been processed, you cannot actively participate in the care of this patient. Nevertheless, your medical curiosity is piqued and you leap to a computer and begin a literature search to see if there is a role for biomarkers to help determine whether this patient would benefit from antibiotics. You develop the following PICO and begin your journey down the rabbit hole.

PICO Question
Population: Adult patients presenting to the Emergency Department meeting SIRS criteria without clear source of infection.
Intervention: Use of procalcitonin to identify patients with bacterial sepsis
Comparison: Standard management
Outcome: Diagnosis of sepsis due to bacterial infection

Search Strategy

You access PubMed and search the Clinical Queries tool using the terms "procalcitonin AND sepsis" with the narrow filter applied (**http://tinyurl.com/pya5gs7**). This results in 261 articles, from which you choose the following four, including recent meta-analysis on the topic.

Article 1: Wacker C, Prkno A, Brunkhorst FM, Schlattmann P. Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. Lancet Infect Dis. 2013 May;13(5):426-35. Answer Key.

Article 2: Jaimes FA, De La Rosa GD, Valencia ML, Arango CM, Gomez CI, Garcia A, Ospina S, Osorno SC, Henao AI. A latent class approach for sepsis diagnosis supports use of procalcitonin in the emergency room for diagnosis of severe sepsis. BMC Anesthesiol. 2013 Sep 19;13(1):23. Answer Key.

Article 3: Tsalik EL, Jaggers LB, Glickman SW, Langley RJ, van Velkinburgh JC, Park LP, Fowler VG, Cairns CB, Kingsmore SF, Woods CW. Discriminative value of inflammatory biomarkers for suspected sepsis. J Emerg Med. 2012 Jul;43(1):97-106. Answer Key.

Article 4: Loonen AJ, de Jager CP, Tosserams J, Kusters R, Hilbink M, Wever PC, van den Brule AJ. Biomarkers and molecular analysis to improve bloodstream infection diagnostics in an emergency care unit. PLoS One. 2014 Jan 27;9(1):e87315. Answer Key.

Bottom Line

Sepsis is defined as the presence of a systemic inflammatory response syndrome (SIRS) in the presence of an infectious etiology. Sepsis is often thought of as the result of a severe infection, resulting in a systemic inflammatory response syndrome (Stearns-Kurosawa 2011). In reality, sepsis represents a clinical spectrum of disease, ranging from a relatively mild immune response to devastating global systemic inflammation leading to vasodilation, hypoperfusion, and multi-organ system failure (Odeh 1996).

While patients on the milder end of the spectrum frequently fare well, mortality in those with severe sepsis and septic shock approached 50% in the late 1990's (Rivers 2001). Even with the advent of early-goal directed therapy, and an increased recognition of the severity of these illnesses and need for timely intervention, mortality remained between 30 and 40% in the following decade(Ferrer 2008, Levy 2010, Castellanos-Ortega 2010). More recent evidence from the newly published ProCESS trial suggests that mortality is now closer to 20%, though this study was performed in academic centers in the US, and some are concerned that a Hawthorne effect may have contributed to this low mortality.

Regardless of the exact cause of this decreased mortality, it seems likely that earlier recognition of disease and initiation of aggressive management has led to improved outcomes in these sicker patients. For example, research has demonstrated decreased mortality associated with earlier administration of antibiotics (Gaieski 2010) and larger volume of fluid administered in the initial 3 hours (Lee 2012). Early diagnosis of sepsis, and differentiation from SIRS due to a non-infectious etiology is therefore critical in the management of these patients.

Early differentiation would benefit not only those patients with severe sepsis and septic shock, but could also improve outcomes in those ultimately diagnosis with a non-infectious etiology. In one study of severe non-infectious SIRS in the ICU, mortality was found to be similar to that in severe sepsis (Dulhunty 2008). While a large proportion of cases identified were either post-operative or trauma-related, and may be more easily differentiated from severe sepsis, many were due to underlying cardiovascular, pulmonary, GI, and neurologic conditions. Diagnosing such patients with severe sepsis, and treating them as such initially, has the potential to delay diagnosis and definitive treatment of the true underlying etiology. Additionally, the administration of broad-spectrum antibiotics in such cases would be of no therapeutic benefit, and may in fact be harmful. Data from the CDC indicate that the use of antibiotics confer a relative risk of developing of a *C. difficile* infection of 3.1 (95% CI 2.5 to 3.8), and suggest that a 30% decrease in the use of broad-spectrum antibiotics would reduce *C. difficile* infection rates by 26%.

Unfortunately, the differentiation of sepsis from non-infectious SIRS can be difficult, particularly in the early phase of the disease. As a result, several biomarkers, most notably procalcitonin, have been proposed as a means of making this differentiation. Procalcitonin is the peptide precursor of calcitonin. Its production is stimulated by endotoxins and cytokines, and is inhibited by interferon-gamma, a cytokine produced by viral infections. As a result, procalcitonin has been proposed as a means of differentiating bacterial infections from both viral infections and non-infectious pro-inflammatory conditions (Delevaux 2003).

We identified 4 articles looking at the use of procalcitonin specifically to distinguish sepsis from SIRS of non-infectious etiology. Three of the studies involved primary research conducted on Emergency Department (ED) patients (Tsalik 2012, Jaimes 2013, Loonen 2014), while the fourth was a systematic review and meta-analysis (Wacker 2013). Sensitivities were poor in the primary studies, ranging from 55% to 68%; specificity fared only slightly better, as low as 64% in one study, and as high as 97% when a higher cut-off was used (sacrificing sensitivity, which decreased to 18%). The sensitivity and specificity in the meta-analysis were 77% and 79%. The resulting likelihood ratios, reported in Table 1, indicate that the probability of sepsis changes very little with procalcitonin results. Some have suggested 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, such a role has not been well-defined, and no clinical decision rules involving procalcitonin have been developed to assist in sepsis diagnosis. 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.

The meta-analysis we reviewed unfortunately suffered from a large degree of heterogeneity. Clinically, the included studies were conducted in a variety of settings, including pediatric, medical, and surgical ICUs, hospital wards, and the ED. Additionally, the studies evaluated procalcitonin using a wide range of cut-offs, 0.1 to 15.75 ng/mL, making interpretation of the reported test characteristics difficult.

Table 1. Diagnostic accuracy of procalcitonin

Study • Cut-off	AUC (95% CI)	LR+	LR-
Jaimes • 0.3 ng/mL	0.69 (0.65-0.72)	1.77	0.57
Tsalik • 0.1 ng/mL • 0.5 ng/mL • 3 ng/mL	0.72 (N/A)	1.9 3.2 6.3	0.51 0.68 0.84
Loonen • (2 ng/mL)	0.81 (0.70-0.91)	3.9	0.52
Wacker • various	0.85 (0.81-0.88)	3.7	0.29

The result was a high degree of reported statistical heterogeneity, with an I^2 of nearly 78% for both sensitivity and specificity, and 96% for the bivariate model. Given this high degree of heterogeneity, it would have made more sense for the authors to report the data of the individual studies without performing a meta-analysis.

Unfortunately, sepsis research in general is handicapped by the lack of a gold standard. Reliance on source testing and culture results leads to high false negative rates, as blood cultures are positive in only around one-fourth of septic patients (Bates 1997). Diagnostic research on sepsis therefore relies on expert opinion and consensus to differentiate septic from non-septic patients. While there are methods to attempt to correct for the absence of a true gold standard (Reitsma 2009, Rutjes 2007), including the use of panel consensus as employed in our studies, these methods are lacking in methodological research. Despite the moderate to high rates of agreement noted in the studies by Jaimes and Tsalik (65% and 82%, respectively), this reference standard is far from perfect. Evaluation of the diagnostic accuracy of a test depends on how well the results of the test in question agree with outcomes based on the gold standard. When the reference standard is imperfect, the resulting test characteristics (sensitivity, specificity, likelihood ratios) are less reliable.