Sick or Not Sick? : Evolving Biomarkers for Severe Bacterial Infection

NEW CONCEPTS AND EMERGING TECHNOLOGIES FOR EMERGENCY PHYSICIANS

Dear Colleagues:

Emergency physicians see, diagnose, and treat patients with severe bacterial infections on every shift. Advances in the understanding of mammalian biochemistry, immunology, and physiology offer new pathways by which we can understand and diagnose this complex disease process. The improved sophistication of laboratory methods offers the rapid detection of biomarkers previously only available through reference laboratories.

Through this publication, we seek to provide the most up-to-date evidence on biomarkers for serious bacterial infection. Some of these biomarkers will be familiar to you while others may provide new insights into the diagnosis and treatment of this population. It is critical for EMCREG-International and the author of this manuscript that this publication reflects the best available evidence. The literature presented within proportionally represents the new knowledge on this topic.

Through this Newsletter, we strive to provide you with new practical information to use on your next clinical shift or in the education of tomorrow's emergency medicine specialists. We hope you enjoy reading this Newsletter and participating in the many other EMCREG-International CME activities.

Sincerely,

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Objectives:

1) Describe the attributes of the ideal clinical biomarker.
2) List potential new biomarkers that can be used to aid in the diagnosis, risk stratification, and treatment of severe bacterial infection.
3) Compare the limitations of each biomarker in the emergency department clinical setting.

Knowing the Problem

In the United States, sepsis accounts for over 751,000 cases, 215,000 deaths, and 16.7 billion dollars in health care costs annually. Severe sepsis kills more individuals than breast, colon, rectal, pancreatic, and prostate cancer combined.[1-3] With the difficulties associated with access to primary care and more aggressive emphasis on rapid hospital discharge and outpatient surgeries, sepsis ranks as one of the highest prevalence, highest mortality, and most expensive conditions that an emergency physician (EP) will encounter. Recent emphasis on goal-directed resuscitation and new aggressive treatment adjuncts such as intensive insulin therapy, activated protein C, and steroid therapy stand to improve outcomes in this common emergency condition.[2] Emergency physicians have a magnificent opportunity to significantly impact this critically ill patient population.

Sepsis and the preceding severe bacterial infection (SBI) can cause significant challenges for EPs. These
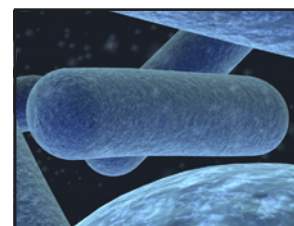
We can expect a rise in the incidence of SBIs due to increases in antibiotic resistance, nosocomial infections, the ageing population, invasive procedures, and life extending medical care.

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infections may have occult presentations and potentially life threatening consequences for the patient. We can expect a rise in the incidence of SBIs due to increases in antibiotic resistance, nosocomial infections, the ageing population, invasive procedures, and life extending medical care. These complex diseases can be caused by bacterial, viral or fungal infections or parasitic infestations and can be made worse by trauma, burns, surgery, increased age, comorbid illness, and immunocompromise. The rapid diagnosis, risk stratification, and treatment of SBIs are central to the mission of emergency medicine and the health care system as a whole. Despite significant advances in resuscitation and antimicrobials, the morbidity and mortality for severe sepsis and septic shock remain extremely high. In the last several years, EPs have taken a central role in the clinical care and academic evolution of this disease entity. Patients will benefit from these efforts to provide rapid diagnosis and appropriate aggressive treatment leading to improved outcomes.[4,5]

The Challenge of Diagnosis

Diagnosing SBI can be difficult because signs and symptoms are variable depending on the nature and stage of the infection. Typical SBI features such as fever, high white blood cell count, and tachycardia can be caused by a variety of conditions. Even patients with overt sepsis may not manifest all the typical features of the syndrome. The microbial etiology of SBI is often not apparent and even positive cultures may be the result of contamination. Up to 35% of sepsis patients have no identified microbiological agent and therefore, diagnosis and empiric therapy have to be based on other parameters. [1,5, 6] The major challenges are to make the diagnosis of SBI, appropriately disposition high-risk patients, and not indiscriminately admit patients for unnecessary tests and costly treatment. The lack of specific diagnostic criteria and the inherent inability to have immediate culture results makes the search for sensitive and specific diagnostic biomarkers for SBI of paramount importance.

The Future of Biomarkers for SBI

In seeking the ideal marker or laboratory test for SBI, there are several important considerations. The "perfect" biomarker for SBI would:

- Have a good positive and negative predictive value
- Stratify patients as to the severity of infection
- Have a defined cut-off value for diagnosis
- Risk stratify patients for appropriate disposition
- Change or support therapeutic decision making
- Monitor progress of disease and response to therapy
- Improve ED and hospital resource utilization

Sepsis represents only a subset of patients with SBI and is characterized by a general inflammatory response which can alter physiologic features such as hemodynamic parameters and coagulation (Figure 1). Many of the physiologic derangements are caused by the host's response to infection rather than the infectious agent itself. The body reacts to the invading organism through cellular activation, up-regulation of specific cell markers, release of cytokines and acute phase proteins, and activation of the complement pathway resulting in a complex interplay between mediators of the inflammatory cascade. Most currently investigated biomarkers of SBI are a component of this aggressive response to host invasion (Figure 2 and Table 1).

Table 1

| Potential biomarkers for SBI |
|---|
| • Lactate |
| • Troponin (Tn) |
| • Vascular endothelial growth factor (VEGF) |
| • Platelet derived growth factor (PDGF) |
| • Cortisol |
| • Proadrenomedullin |
| • Macrophage migratory inhibitory marker (MIF) |
| • Activated protein C (APC) |
| • CD 4, CD 8, CD 13, CD 14, CD 64 |
| • Caspase |
| • Placental growth factor (PlGF) |
| • Calcitonin gene-related peptide (CGRP) |
| • High-mobility group 1 protein (HMG-1) |
| • C reactive protein (CRP) |
| • White blood cell count (WBC) |
| • Procalcitonin (PCT) |
| • Natriuretic peptides (BNP and ANP) |
| • Interleukins 1, 6, 8, 10 (IL) |
| • Copeptin |
| • Tumor necrosis factor alpha (TNF-a) |
| • Liposaccharide binding protein (LBP) |
| • Circulating endothelial progenitor cells (EPC) |
| • Complement 3a (C3a) |
| • Triggering receptor expressed on myeloid cells (TREM-1) |
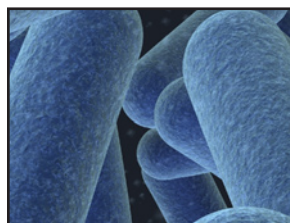
Most new biomarkers and potential biomarkers for SBI are components of the inflammatory response system
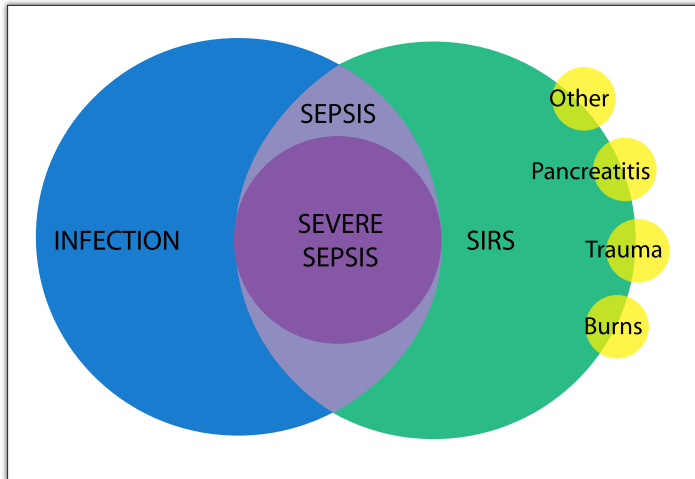
Figure 1: Relationship of the components of severe bacterial infection. SIRS = systemic inflammatory response syndrome

Biomarkers for SBI: Old Standbys and New Favorites?

Emergency cardiovascular care has enjoyed the benefits of sensitive and specific biomarkers for many disease processes such as acute coronary syndromes (ACS) and acute decompensated heart failure (ADHF). The cardiac troponins and brain natriuretic peptides (BNP) are widely used in the emergency department (ED) for diagnosis, prognosis, and treatment.[7,8] In these clinical conditions, the "gold standard" for these biomarkers is easier to define than for SBI. For instance, an acute coronary syndrome (ACS) diagnosis might be supported by coronary artery catheterization and ADHF might be substantiated by an echocardiogram. In SBI, there is no such standard and the diagnosis may depend on a combination of cultures, signs and symptoms, radiographs, or even other biomarkers, each of which has its own limitations. Many reports, publications, and presentations have examined a variety of potential biomarkers for SBI but their utility and uptake into clinical practice have been variable.
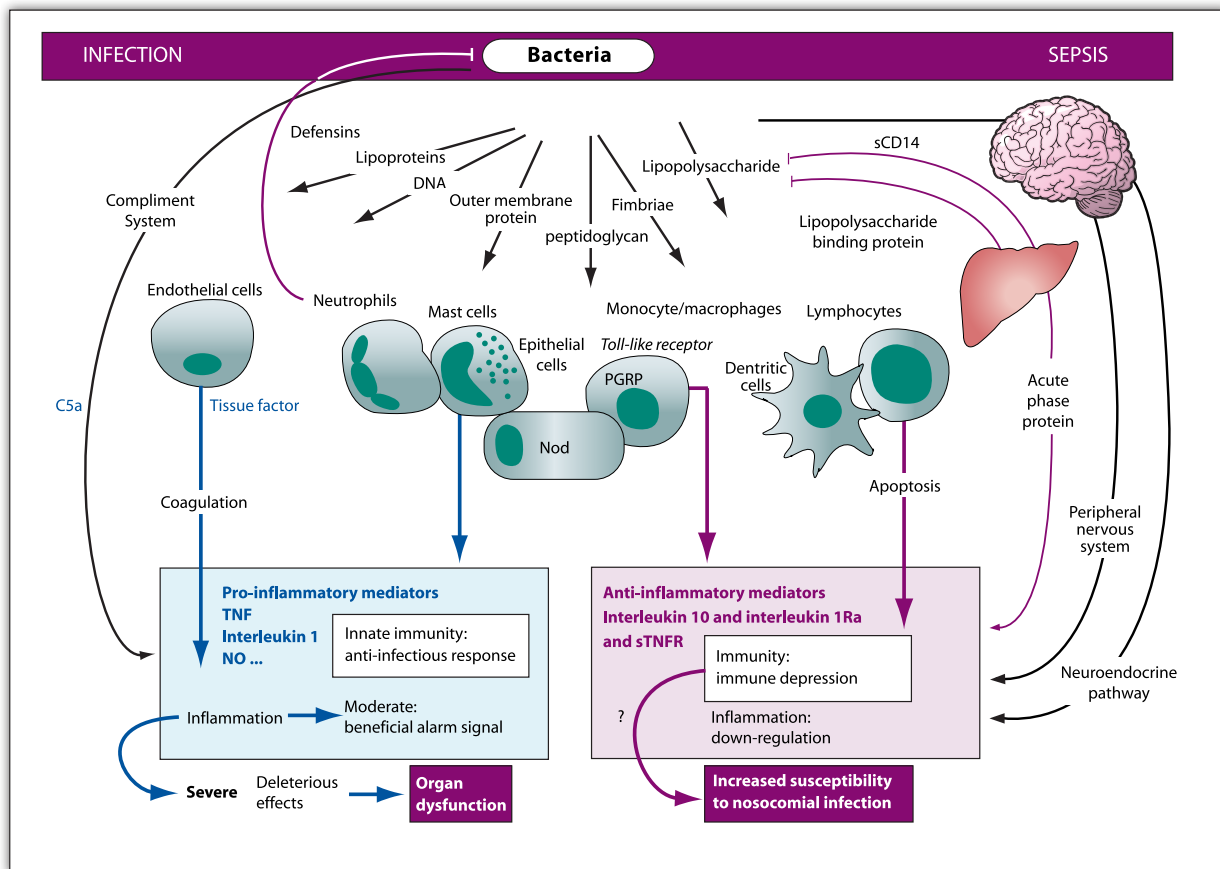
Figure 2: Components of the inflammatory cascade and source of new biomarkers for SBI. Adapted with permission from Annane et al., Lancet. 2005;365(9453):63-78.

WBC and Cell Surface Markers

The white blood cell (WBC) count is probably the most commonly recognized biomarker for the consideration of SBI. An elevated WBC may be suggestive of an infection, but cannot be used in isolation to appropriately risk stratify patients. Acute trauma, burns, seizures, and some medications also can have a significant effect on the WBC. Nonetheless, criteria for systemic inflammatory response syndrome (SIRS) include a WBC $\geq$14,000 or $\leq$4000 cells/mm^3, or a bandemia >10%, yet this value is taken in the context of several other parameters.[2] Recent studies using sophisticated flow cytometry have examined specific cell types and surface markers. The increase or decrease of surface receptors such as CD4, CD8, CD13, CD14, and CD64 on certain subpopulations of monocytes and lymphocytes have variable predictive values for SBI and commensurate morbidity and mortality[9-12]. While this information provides a promising outlook on the future of SBI diagnosis, the laboratory techniques and limitations of detecting these cell subtypes restricts their usefulness in the ED setting at this time.

Cytokines

Cytokines, a component of the innate immune system, are secreted in response to severe physiologic challenges such as bacterial infections, trauma and burns. They can be pro- or anti-inflammatory and regulate the immune system by promoting or inhibiting cellular activation. Tumor necrosis factor alpha (TNF-α) and the interleukins (IL-1, IL-6, IL-8, and IL-10) are the most studied of the inflammatory cytokines. Previous studies in neonates demonstrated high sensitivity but low specificity of IL-6, IL-8, and TNF-α; studies in adults have shown similar results.[13-15] More recently, Livaditi et al. measured IL-8, IL-1β, IL-6, IL-10, IL-12p70, tumor necrosis factor-α (TNF-α), CD64, and other biomarkers in 47 critically ill patients within 24 hours of symptom onset. CD64 and IL-8 demonstrated the most promising sensitivity and specificity for predicting sepsis stages and 28-day mortality.[16] Cytokines have been extensively studied and have resulted in several publications showing positive results. The variability in the time course and individual patient kinetics for secretion limit their use for diagnosis, but may serve to monitor patients over time. Presently, cytokine measurements lack the necessary sensitivity and specificity needed in the ED environment.[17-19]

C-reative Protein

C-reactive protein (CRP) is an acute phase reactant and indicates the non-specific presence of an acute inflammatory state. Like its cytokine relatives, CRP has been extensively studied and is of historical interest as one the first clinically utilized and most widely studied inflammatory biomarkers.[20, 21] Most studies agree that CRP is sensitive for bacterial infection but lacks specificity.[19] Current literature shows a positive role for the use of CRP in diagnosing acute bacterial infection, but most authors support the use of CRP in combination with other more acute biomarkers or for monitoring of therapy.[16,19, 22,23] The concentration of CRP parallels the course of infection and its appropriate contemporary use will be to determine when to discontinue antibiotic therapy and monitor long term treatments such as those for osteomyelitis.[24] Exact sensitivities and specificities of CRP for the diagnosis of SBI vary from study to study and therefore EPs should interpret it's elevation in the context of other clinical factors.
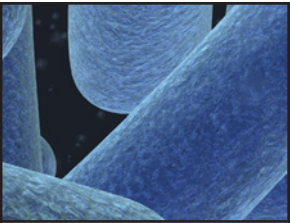
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Lactate

Several studies support the use of serum lactate in both the diagnostic and treatment phases for septic shock.[2,25,26] Lactate is generated from the anaerobic metabolism of pyruvate and signifies cellular hypoperfusion or impaired cellular oxygen utilization. In the Surviving Sepsis Campaign, a lactate level of greater than 4mmol/L is a resuscitation bundle element indicating sepsis induced hypoperfusion and triggers guideline driven early goal directed therapy (EGDT).[5] In a multivariate analysis of over 20 hemodynamic and physiologic variables including pulmonary artery pressures, total blood volume index, mucosal-arterial PCO_2, and gastric intramucosal pH, lactate was found to be the only parameter which could be obtained in the ED that was predictive of outcome.[25]
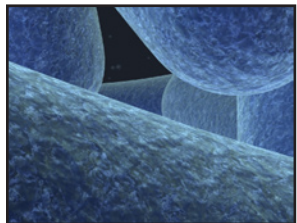
Lactate screening may also prove beneficial in normotensive, hemodynamically stable patients. Shapiro et al. in a study of 1,278 patients with infection demonstrated that increasing lactate levels were associated

Lactate screening may also prove beneficial in normotensive, hemodynamically stable patients

with increased mortality. Lactate levels less than 2.5mmol/L were associated with a 4.9% mortality rate compared to patients with lactate levels >=4mmol/L who had a mortality of 28.4%. A lactate concentration > 4mmol/liter was 36% (95% CI 27-45%) sensitive and 92% (95% CI 90-93%) specific for mortality (Figure 3).[3]
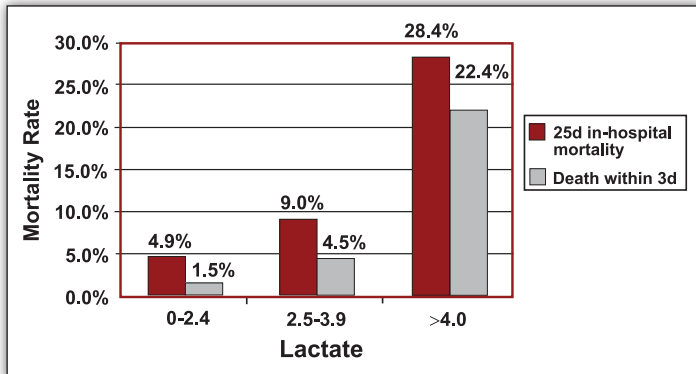
Figure 3: Lactate as a predictor of mortality in patients with infection. Adapted with permission from Shapiro et al., Ann Emerg Med. May 2005;45(5):524-528.

Just as in the trauma population, serial lactate measurements and attention to lactate clearance or "lac-time" may provide additive information useful in the treatment and prognosis of the individual patient. For instance, Bakker et al. found that while initial blood lactates did not differ between survivors and non-survivors in patients with septic shock, survivors had a significant decrease in lactate levels and lower "lac-times."[27] Nguyen et al. examined a cohort of 111 ED and ICU patients with severe sepsis and septic shock. In this study, lactate clearance was defined as the percentage lactate decrease over the initial six hour ED evaluation and treatment period (Figure 4).[28] All patients were followed for 72 hours and received protocol-driven EGDT. Multivariate logistic regression analysis of statistically significant univariate variables showed an inverse relationship with mortality. Patients with higher lactate clearance had lower mortality. In fact, mortality was reduced approximately 11% for each 10% increase in lactate clearance. Patients with a lactate clearance >10% had a greater improvement in Acute Physiology And Chronic Health Evaluation (APACHE II) scores and lower 60-day mortality.[28] These findings suggest an important role for serial sampling of biomarkers with appropriate metabolic parameters in patients with suspected SBI.

Cardiac Biomarkers

Cardiac troponin I and T (cTnI and cTnT) are highly sensitive and specific biomarkers for myocardial cell necrosis.[7] Troponin positivity indicates a worse prognosis and identifies a patient population that best benefits from treatment.[29] It is clear that troponin can be elevated in conditions other than ACS, such as pulmonary embolism, renal failure, and now SBI.[30] Despite the fact that intensive care unit patients with sepsis represent a heterogeneous population with a variety of confounding factors such as baseline cardiac disease, vasopressor use, extreme hypotension and multiorgan dysfunction, elevated troponin levels have been shown to be related to disease severity and short term prognosis.[31-33] Several studies also now show BNP elevations in critically ill septic patients. For instance, McLean et al. showed that BNP levels were elevated in septic patients with normal baseline systolic function. In these patients, the median level was 279 pg/mL (95% CI 110-636).[34] Similar elevations in sepsis patients have been found for N-terminal pro-brain natriuretic peptide (NT-proBNP).[26] SBI diagnosis and treatment cannot rely on individual cardiac biomarkers alone, but can alert clinicians of a more severe disease state.

$$\text{Lactate Clearance} = \frac{(\text{Lactate}^{\text{ED Presentation}}) - (\text{Lactate}^{\text{Hour 6}})}{\text{Lactate}^{\text{ED Presentation}}} \times 100$$

Figure 4: Definition of lactate clearance. Adapted with permission from Nguyen et al., Crit Care Med. Aug 2004;32(8):1637-1642.

Procalcitonin

The predominance of contemporary literature on the marker diagnosis of SBI includes studies of CRP, lactate, procalcitonin (PCT), and the interleukins. In the last few years, studies with PCT in patients presenting with acute illness has earned the increasing attention of EPs. PCT is the precursor hormone for calcitonin and is normally secreted by the C-cells of the thyroid gland. During times of severe infection, PCT is also synthesized by peripheral tissues and blood. Now
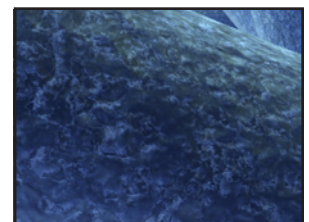
Most of the research performed on PCT has occurred in Europe where this test has been used for diagnosis and treatment of critically ill patients for over a decade.

referred to as a "hormokine," numerous studies have shown that PCT is significantly increased in septic states and correlates with both the severity of infection, response to treatment and prognosis.[35-38] Most of the research performed on PCT has occurred in Europe where this test has been used for diagnosis and treatment of critically ill patients for over a decade. Hence, most of the supporting literature for PCT is published in journals unfamiliar to EPs in the United States.

PCT has been most extensively studied in respiratory tract infections where it has been used to diagnose, risk stratify, and treat critically ill community acquired pneumonia (CAP) patients and decrease unnecessary antibiotic use in less severe lower respiratory tract infections (LRTIs). In one study of 545 patients, 373 with CAP, 132 other respiratory tract infections, and 40 with other diagnoses, PCT had a higher diagnostic accuracy (AUC, 0.88 [0.84-0.93]) in diagnosing CAP, as compared to hsCRP (AUC, 0.76 [0.69-0.83]; p < 0.001) and total leukocyte count (AUC, 0.69 [95% CI 0.62-0.77]; p < 0.001) (Figure 5). PCT had a greater AUC (0.85 [0.80-0.91]) as compared to hsCRP (p = 0.01), leukocyte count (p = 0.002) and elevated body temperature (p < 0.001) in predicting bacteremia. PCT, in contrast to hsCRP and leukocyte count, increased with increasing severity of CAP as assessed by the pneumonia severity index (p < 0.001).[39] An additional European study sought to determine if PCT could be used to decrease antibiotic use in LRTI. For this trial, one group of physicians prescribed antibiotics based on PCT levels (Figure 6) whereas the other prescribed antibiotics per usual clinical practice. Clinical outcomes in both groups were similar. PCT guidance of antibiotic therapy was associated with less antibiotic use (83% vs. 44%) and an adjusted relative risk of antibiotic exposure of 0.49 (CI 0.44-0.55; p<0.0001).[40]

PCT (0.88; 0.84-0.93)   CRP (0.76; 0.69-0.83)
Leukocytes (0.69; 0.62-0.77)   Temperature (0.55; 0.46-0.63)
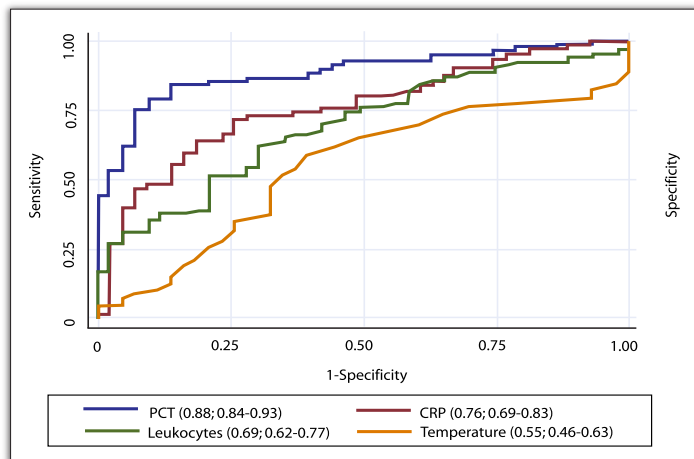
Figure 5: Diagnostic accuracy to predict radiographically suspected CAP. Adapted with permission from Muller et al., BMC Infect Dis. 2007;7:10.
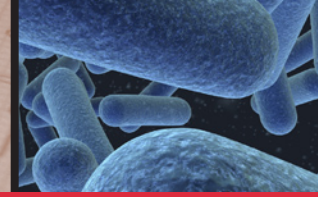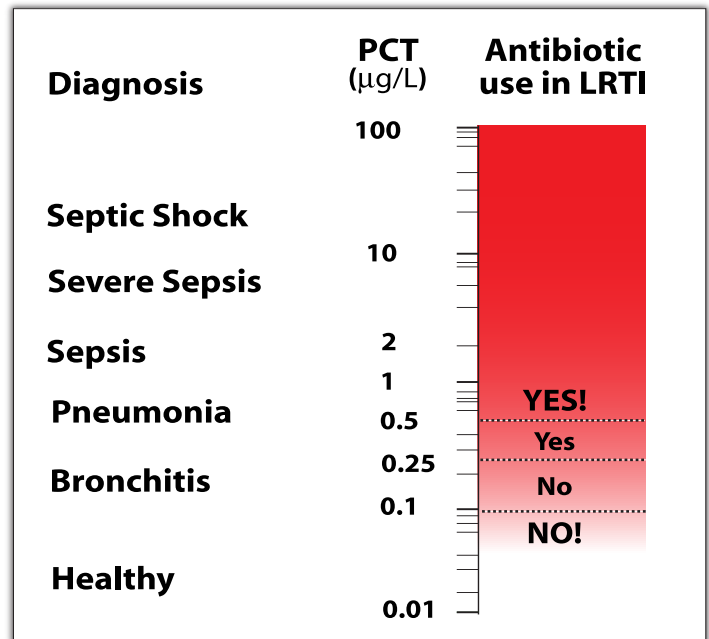

Figure 6: Procalcitonin levels and recommended use of antibiotics in lower respiratory tract infections. PCT=procalcitonin; LRTI=lower respiratory tract infection. Adapted with permission from Christ-Crain et al., Lancet. 2004;363(9409):600-607.

In addition, PCT has been studied in a variety of patient populations with acute disease. Other potential applications for PCT as a biomarker of infection include endocarditis,[41] febrile neutropenia,[42,43] and conditions of immunocompromise such as HIV and post-transplant.[44,45]

Less than a handful of PCT studies have been conducted in ED populations in the United States. In 2004, a brief report (n=108) compared PCT to WBC in elderly patients with suspected sepsis.[46] A PCT >0.2 ng/mL was 93% sensitive (95%CI=79%-100%), 38% specific (95%CI=28-48%), and had a negative likelihood ratio of 0.18 for culture proven bacteremia. The authors concluded a PCT level of 0.2ng/mL was moderately helpful in ruling out bacteremia and was significantly better than the WBC. At the 2006 American College of Emergency Physicians Research Forum, consistent with other European trials, authors concluded that PCT correlated well with clinical presentation and clinical outcomes in CAP and may provide prognostic information beyond PSI in severely ill patients.[47] Most recently, Lee and colleagues demonstrated PCT and the validated Mortality in Emergency Department Sepsis (MEDS) score could be used in combination to accurately predict mortality in septic ED patients.[48]

Two meta-analyses of the diagnostic utility of PCT have come to different conclusions. Jones et al. performed a comprehensive search in which 17 of 348 publications met criteria for review. The unweighted summary receiver-operating characteristic (ROC) curve showed an area under the curve (AUC) of 0.84 (95% confidence interval [CI] 0.75-0.90). A separate subgroup analysis of studies using a test threshold of >4 ng/mL revealed a pooled sensitivity and specificity of 76% and 70%, respectively. These authors determined PCT to be of "moderate" performance and suggested further study in the ED or ambulatory population.[49] Uzzan et al. performed a similar meta-analysis and in addition compared PCT to CRP.[50] They identified 33 studies meeting inclusion criteria comprising 3943 patients. The summary ROC curve for the diagnosis of infection complicated by systemic inflammation was better for PCT than for CRP. The global odds ratio for PCT was 15.7 (95% CI, 9.1-27.1) compared to 5.4 (95% CI, 3.2-9.2) for CRP. These authors concluded that PCT was a "good" diagnostic marker for sepsis, severe sepsis, and septic shock and recommended its use in the ICU setting.

These analyses differed in their study article selection, definition of severe infection, and patient populations. In addition, they spanned over a time period during which assay characteristics were changing. The lack of a "gold standard" and changing assay sensitivities complicate this issue. Older assays may lack the sensitivity to appropriately detect early severe infections. It is clear that no one study or group of studies adequately demonstrates the perfect application for PCT.

In summarizing the findings of the studies available, PCT is a good diagnostic marker and good predictor of severity and outcome. PCT has better test characteristics and may be more helpful than other traditionally used, less specific markers. Other studies in adult ED patients are needed to further define appropriate populations, disease entities, and cut-off values in the United States.
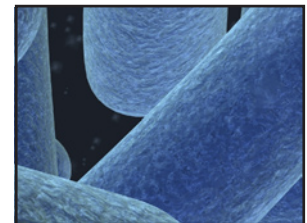
New Biomarkers

New studies appear every month describing new, potential biomarkers for SBI. Most are reports from small human studies or animal models but nonetheless demonstrate active and hopeful research in the area. For instance, circulating endothelial progenitor cells (cEPCs) have been shown to be more elevated in septic intensive care unit patients than in non-septic patients and healthy controls.[51] Vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) are other inflammatory biomarkers that appear to increase in animal and human models of sepsis.[52] Higher platelet derived growth factor-BB (PDGF-BB) levels are associated with increased survival and appear to be a potential

mechanism by which activated protein C (APC) mediates vessel wall homostasis and tissue healing.[53] The release of calcitonin gene-related peptide (CGRP) is stimulated by endotoxin and the extent of rise has been correlated with outcome.[54] Lipopolysaccharide binding protein (LBP) may be used with other biomarkers such as IL-6, CRP, and PCT to provide a greater positive predictive value than each marker alone.[55] Pro-adrenomedullin, co-peptin, and cortisol are also possible biomarkers in the future.[36] Further studies are underway investigating molecular techniques and differential gene expression.[56, 57] All these new biomarkers have promising initial results yet none are ready for or readily available in the ED setting.

Conclusion

There are several biomarkers available for the diagnosis, prognosis, and therapeutic response of SBI. At the present time only the WBC, lactate, CRP, IL-6 and IL-8, and PCT have testing platforms which provide results in the time needed for ED care. CRP and WBC have already been extensively used in the ED environment. Lactate has re-emerged as a useful marker for infection and trauma. IL-6 and IL-8 have potential to follow the time course of infection and effect of treatment for an individual patient, but at present lack the sensitivity and specificity for diagnosis. Lastly, PCT has a growing body of evidence in Europe but has not become routinely used for care yet in EDs within the United States. The field of emergency medicine needs to advance diagnostic methods and algorithms for this truly critically ill patient population. The success of these biomarkers will depend on the determination of the appropriate patient populations and cut-off ranges for particular clinical conditions. The near-term future will likely bring SBI marker panels and diagnostic "scores." Only when EPs grow comfortable with data from quality studies and through the experience of using new markers in conjunction with older ones will we see a change in the way SBI is diagnosed and treated. By diagnosing SBI early and efficiently, EPs will improve care and outcomes by identifying patients in need of acute care, monitoring therapeutic response, restricting antibiotic usage, and allocating resources most appropriately.
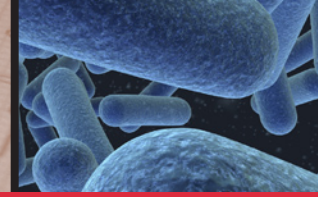
> **Biomarkers are not able to identify the offending organism or give information about antibiotic susceptibility. They must be used together with the clinical assessment.**

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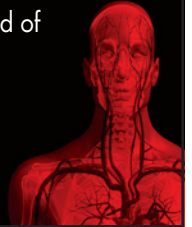
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1. **Favorable emergency department diagnostic test characteristics include all of the following, except:**
   a. Rapid turn around time and diagnostic accuracy
   b. Accessibility to results in the ED
   c. Supports therapeutic decision making
   d. Allows assessment of severity of disease
   e. All of the above

2. **Severe sepsis kills more individuals than breast, colon, rectal, pancreatic, and prostate cancer combined.**
   a. True   b. False

3. **Factors that contribute to an increased incidence of severe bacterial infections include:**
   a. Increasing age of the population
   b. Antibiotic resistance
   c. Increasing numbers of invasive procedures
   d. Increased number of drugs and conditions that affect the immune system
   e. All of the above

4. **Potential new biomarkers for the diagnosis or risk stratification of SBI in the ED include all of the following, except:**
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