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Combined biomarkers discriminate a low likelihood of bacterial infection among surgical intensive care unit patients with suspected sepsis

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ABSTRACT

Among surgical intensive care unit (SICU) patients, it is difficult to distinguish bacterial sepsis from other causes of systemic inflammatory response syndrome (SIRS). Biomarkers have proven useful to identify the presence of bacterial infection. We enrolled a prospective cohort of 69 SICU patients with suspected sepsis and assayed the concentrations of 9 biomarkers (α-2 macroglobulin [A2M], C-reactive protein, ferritin, fibrinogen, haptoglobin, procalcitonin [PCT], serum amyloid A, serum amyloid P, and tissue plasminogen activator) at baseline, 24, 48, and 72 hours. Forty-two patients (61%) had bacterial sepsis by chart review. A2M concentrations were significantly lower, and PCT concentrations were significantly higher in subjects with bacterial sepsis at 3 of 4 time points. Using optimal cutoff values, the combination of baseline A2M and 72-hour PCT achieved a negative predictive value of 75% (95% confidence interval, 54–96%). The combination of A2M and PCT discriminated bacterial sepsis from other SIRS among SICU patients with suspected sepsis.

1. Introduction

It is difficult to distinguish bacterial sepsis from other causes of systemic inflammatory response syndrome (SIRS) in critically ill patients. The presence of 2 or more SIRS criteria with suspected infection has become the standard for sepsis diagnosis (ARISE Investigators et al., 2014; COIITSS Study Investigators et al., 2010; Holst et al., 2014; Mouncey et al., 1992; Opal et al., 2013; Perner et al., 2012; Ranieri et al., 2012; Sprung et al., 2008). However, the SIRS criteria have been criticized for lacking specificity for infection (Levy et al., 2003; Liao et al., 2014; Sprung et al., 2006; Vincent, 1997; Vincent et al., 2013). Given the morbidity and mortality associated with bacterial sepsis as well as evidence that early antibiotic therapy improves mortality in severe sepsis, guidelines recommend that empiric, broad-spectrum antibacterial agents be administered to patients who meet the 2-SIRS-criteria standard (Kaukonen et al., 2015; Brun-Buisson et al., 2004; Gaieski et al., 2010, 2013; Dellinger et al., 2013; Ferrer et al., 2014). The poor specificity of the SIRS criteria may thus contribute to excess use of broad, empiric antibiotics.

Surgical intensive care unit (SICU) patients, in particular, represent a population in whom SIRS criteria may demonstrate poor specificity for bacterial infection. The incidence of SIRS in the SICU exceeds the incidence in medical and cardiovascular intensive care units (ICUs). Prior studies have shown that greater than 90% of SICU patients meet SIRS criteria during their ICU stay (Pittet et al., 1995; Sigfrido Rangel-Frausto et al., 1995). The SICU has a higher proportion of culture-negative SIRS and sepsis than do medical or cardiovascular ICUs (Sigfrido Rangel-Frausto et al., 1995; Andersson and Tracey, 2011; Vincent et al., 2013).

Biomarkers have proven to be useful tools to distinguish the presence or absence of bacterial infection in specific patient populations. Procalcitonin (PCT) in particular has shown promise as a component of diagnostic and antibiotic stewardship strategies for respiratory tract infection and sepsis (Assicot et al., 1993; Schuetz et al., 2009, 2012a, 2012b, 2013; Christ-Crain et al., 2004; Simon et al., 2004; Uzzan et al., 2006; Tang et al., 2007; Nobre et al., 2008). A combination of biomarkers may be even more useful than a single biomarker by increasing specificity

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for infection and improving the ability to discriminate true bacterial sepsis from other causes of SIRS (Meisner et al., 1999; Harbarth et al., 2001; Castelli et al., 2004). To date, studies of biomarkers in sepsis have been limited in the number of biomarker combinations evaluated, and few studies have restricted analysis to SICU patients, a population in whom bacterial sepsis may be more difficult to discriminate (Hensel et al., 1998; Meisner et al., 1998; Uzzan et al., 2006; Castelli et al., 2009; Prkno et al., 2013; Wacker et al., 2013). The identification of SICU patients in whom antibacterial therapy can be safely stopped has the potential to aid antibiotic stewardship efforts, avoid adverse drug effects, and combat the evolution of drug-resistant pathogens (Fishman, 2006; Dellit et al., 2007; Roberts et al., 2009; Luyt et al., 2014). We designed this study in companion with a study of biomarker performance in medical ICU (MICU) patients with suspected sepsis (Han et al., 2015), with the hypothesis that optimal biomarker combinations and cutoffs may be specific to the SICU population.

We sought to systematically evaluate the ability of 9 biomarkers, individually and in combination, to distinguish bacterial sepsis from other causes of SIRS in SICU patients. We further sought to define optimal biomarker cutoffs and sampling times to identify SICU patients with a low likelihood of bacterial infection.

2. Materials and methods

2.1. Study design and setting

We prospectively enrolled patients admitted to the SICU of the Hospital of the University of Pennsylvania from February 2012 to May 2014. The study was approved by the institutional review board of the University of Pennsylvania. Because residual blood from routine clinical samples was used for biomarker analysis, a waiver of informed consent was granted.

2.2. Study population

Patients were deemed eligible for study enrollment if they were identified as having presumed bacterial sepsis, defined by meeting 2 or more SIRS criteria and having new empiric antibiotic therapy initiated and blood cultures ordered within a 4-hour window (Bone et al., 1992; Levy et al., 2003), at SICU admission or at any time during the SICU stay. Two or more SIRS criteria (body temperature >38 °C or <36 °C, heart rate >90/minute, respiratory rate >20/minute, or white blood cell count >12,000 cells/μL or <4000 cells/μL) had to be met within 4 hours of the enrollment blood culture. Patients were ineligible if new or broadened empiric antibiotic therapy had been given for greater than 4 hours past the time point when baseline biomarkers were measured given the potential for antibiotic therapy to impact baseline PCT measures (Meisner, 2014). New empiric antibiotic therapy was defined as the initiation of new antibiotic therapy in a patient previously not on any antibiotics or broadening of antibiotic therapy in a patient already receiving an antibiotic. Antibiotic review was performed by a physician trained in infectious diseases (E.L.).

SICU patients with presumed bacterial sepsis, defined as above, were excluded from enrollment if they had 1) a code status of "do not resuscitate", 2) cardiopulmonary arrest from which they had been resuscitated, 3) documented bacterial infection treated with antibacterial therapy in the five days prior to enrollment, or 4) evidence of immune compromise (including human immunodeficiency virus infection with CD4 cell count <200 cells/mm^3, immunosuppressive therapy after organ transplantation, neutropenia [<500 neutrophils/mm^3], chemotherapy, receipt of ≥20 mg/d of prednisone for 2 or more weeks in the preceding 3 months, or cystic fibrosis). These exclusions were made because the use of biomarkers to identify low risk for bacterial infection (and potentially discontinue empiric antibiotics) was believed to be less useful in patients in whom antibiotic management would be dictated by code status, established bacterial infection, or an a priori high risk of bacterial infection (i.e., immunocompromise).

2.3. Biomarker measurements

Serum samples for biomarker measurements were obtained from residual blood samples from tests performed for routine clinical care and stored at −70 °C until testing as previously described (Han et al., 2015). Baseline biomarker measurements were performed at the time a patient met all eligibility criteria. Measurements were repeated daily for 3 days (24-hour, 48-hour, and 72-hour time points). If multiple clinical blood samples were available, the one closest to the precise time point of interest was chosen.

Nine biomarkers were measured at each time point: PCT using the VIDAS BRAHMS PCT assay (bioMérieux, Durham, NC, USA), a 1-step immunoassay sandwich method with fluorescent detection, and the remaining 8 (Supplementary Table 1) using the Bio-Plex Pro™ Human Acute Phase 5- and 4-Plex Panel Complete Kit (Bio-Rad Laboratories, Hercules, CA, USA), a bead-based (xMAP technology) multiplex assay that allows for the simultaneous measurement of 9 positive acute phase biomarkers in serum. Assays were performed per manufacturer's instructions. The Bio-Plex assay was read using a Luminex 200 reader (Luminex Corporation, Austin, TX, USA), with samples from all 4 time points included in the same measurement test run, using a single lot of reagents, and each analyte measured in duplicate (results recorded as the mean of measurements).

2.4. Data collection

Demographic information, comorbidities, and length of hospital and SICU stay before enrollment were recorded at baseline. Comorbidities of interest included hepatic dysfunction (defined as 2 or more of total bilirubin >2.5 mg/dL, aspartate aminotransferase or alanine aminotransferase greater than twice the upper limit of normal), solid or hematologic malignancy, diabetes mellitus, chronic kidney disease (with or without requiring hemodialysis), and pulmonary disease (chronic obstructive pulmonary disease or chronic bronchitis). Acute Physiology and Chronic Health Evaluation II (APACHE II) scores were calculated for patients at enrollment for all subjects in whom parameters were documented (Knaus et al., 1985).

2.5. Definition of infection

The diagnosis of bacterial infection was determined retrospectively by the investigators using established Centers for Disease Control and Prevention (CDC) criteria (Horan et al., 2008). Two physicians trained in infectious diseases (E.L. and J.H.H.) independently reviewed the subjects' cumulative medical records, including all vital signs, provider notes, and laboratory and radiographic results at 72 hours after enrollment. The reviewers were blinded to the results of biomarker testing. In cases of discordant assessments, the 2 reviewers discussed the case and made a consensus determination. The determination of bacterial infection by 2-physician review served as the gold standard against which biomarker test characteristics were assessed. Two-physician review was chosen as the gold standard rather than positive blood cultures given the potential for false-positive or false-negative blood cultures.

2.6. Statistical analysis

We first visually explored the temporal trends in biomarker values, in aggregate and stratified by bacterial sepsis versus other causes of SIRS (i.e., nonbacterial sepsis or noninfectious SIRS) using LOESS regression (with both least-squares estimator and Tukey's biweight M-estimator, the latter to limit the impact of outliers). We then compared the mean biomarkers values between bacterial sepsis versus other SIRS groups at each time point using the Wilcoxon rank sum test. We characterized the clinical characteristics of SICU patients with bacterial sepsis

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