CME/SAM

Procalcitonin as a Marker for the Detection of Bacteremia and Sepsis in the Emergency Department

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Upon completion of this activity you will be able to:
- recognize the complexity and challenges of diagnosing sepsis in patients presenting to the emergency department.
- describe the role of clinical and systemic inflammatory response syndrome (SIRS) criteria in the diagnosis of sepsis.
- describe the relation between procalcitonin and clinical/SIRS criteria in the diagnosis of sepsis.
- discuss the role of procalcitonin and proposed cutoff values for diagnosing sepsis in patients presenting to the emergency department.

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Questions appear on p 310. Exam is located at www.ascp.org/ajcpcme.

Abstract

Rapid diagnosis of bloodstream infections (BSIs) in the emergency department (ED) is challenging, with turnaround times exceeding the timeline for rapid diagnosis. We studied the usefulness of procalcitonin as a marker of BSI in 367 adults admitted to our ED with symptoms of systemic infection. Serum samples obtained at the same time as blood cultures were available from 295 patients. Procalcitonin levels were compared with blood culture results and other clinical data obtained during the ED visit. Procalcitonin levels of less than 0.1 ng/mL were considered negative; all other levels were considered positive. In 16 patients, there was evidence of BSI by blood culture, and 12 (75%) of 16 patients had a procalcitonin level of more than 0.1 ng/mL. In 186 (63.1%) of 295 samples, procalcitonin values were less than 0.1 ng/mL, and all were culture negative. With a calculated threshold of 0.1475 ng/mL for procalcitonin, sensitivity and specificity for the procalcitonin assay were 75% and 79%, respectively. The positive predictive value was 17% and the negative predictive value 98% compared with blood cultures. Procalcitonin is a useful marker to rule out sepsis and systemic inflammation in the ED.

More than 500,000 bloodstream infections (BSIs) are reported annually in the United States and are associated with high mortality rates.[1-5] Early diagnosis and implementation of "early goal-directed therapy" are essential components of the international Surviving Sepsis Campaign guidelines[6-9] and result in reduced mortality. Similarly, differentiating sepsis from other noninfectious causes of systemic inflammation is often difficult because fever and leukocytosis have poor sensitivity and specificity in many clinical settings.[8,10-15] Since sepsis cannot often be excluded, empiric antibiotic treatment is commonly prescribed in the acute care setting. Emergency departments (EDs) are often the first point of contact and care for many patients, and early diagnosis of bacteremia is extremely important but a diagnostic challenge.[16,17] Blood cultures (BCs) are the "gold standard" for diagnosis of sepsis.[3] However, test results (Gram-stain results, definitive organism identification, and antimicrobial susceptibility test results) are typically not available for 12 to 48 hours. This delay has prompted the development and evaluation of rapid and molecular tests for inflammatory and other markers of infection.[14,18,19]

An additional challenge in BCs that are obtained in the ED is that they have high rates of false-positive results due to organisms known to be skin contaminants (eg, coagulase-negative staphylococci). Patients admitted with febrile illness and positive BCs due to contaminant organisms undergo unnecessary diagnostic measures, hospitalization, and unwarranted antimicrobial therapy. The ability for more rapid diagnosis of sepsis and accurate assessment of disease severity and mortality risk at the ED admission combined with early initiation of appropriate treatment may have a great impact on outcome.

The observation that the serum procalcitonin level rises above normal values in patients with sepsis and other clinically

significant bacterial infections was first described in 1993 by Assicot et al.[20] The procalcitonin level is not elevated in viral infections. Recent studies, primarily conducted in the critical care setting, have evaluated procalcitonin as a diagnostic tool to define patients with sepsis and systemic inflammatory response syndrome (SIRS).[21-25]

Because procalcitonin analysis can be performed in less than 1 hour, we propose that procalcitonin would have substantial usefulness in the ED setting to assist evaluation of febrile patients at risk for bacteremia and sepsis. In this study, we evaluated the usefulness of procalcitonin as a diagnostic predictive marker of bacteremia and sepsis in the ED in an adult patient population.

Materials and Methods

Study Population and Review of Medical and Laboratory Records

Between January 2008 and March 2009, we evaluated medical records of patients seen in the ED at a university-affiliated, tertiary care medical center (Johns Hopkins Bayview Medical Center, Baltimore, MD), who had BCs obtained in the ED. This study was approved by the Johns Hopkins Institutional Review Board.

Adult patients (18 years or older) with symptoms of systemic infection and/or inflammation for whom a BC was obtained during the initial ED visit were enrolled. Laboratory records were screened for the presence of available, stored blood specimens (serum or EDTA blood) for additional procalcitonin analysis. Blood samples from serum-separator tubes were centrifuged, and an aliquot of the serum was removed and stored at –70°C for procalcitonin analysis. Clinical data were abstracted from the medical records and included age, sex, SIRS criteria (WBC count, body temperature, blood pressure, and heart rate), initial clinical diagnosis by *International Classification of Diseases, Ninth Revision, Clinical Modification* code, and BC results.

An episode of bacteremia or sepsis was defined as the recovery of any significant, pathogenic bacterial species in 1 or 2 sets of BCs (aerobic and anaerobic bottles) obtained in the ED. Organisms commonly considered as BC contaminants (eg, coagulase-negative staphylococci, aerobic and anaerobic diphtheroids, *Micrococcus* sp, *Bacillus* sp) were excluded from this definition.[26] BCs were processed using the VersaTREK continuous BC monitoring system (TREK Diagnostics, Cleveland, OH). Bacteria from positive BCs were further identified using standard laboratory methods. Cultures that did not indicate growth within 5 days of incubation in the VersaTREK system were considered negative.

Procalcitonin Assay Analysis

Following the completion of requested laboratory tests and within 24 hours of sample collection, blood samples from ED patients were centrifuged at 4°C, and a portion of the serum was collected and stored at –70°C. Batched serum samples were analyzed for procalcitonin levels using the Kryptor chemiluminescence immunoassay (BRAHMS, Hennigsdorf, Germany). The assay measures procalcitonin levels in human serum or plasma using a sandwich immunoassay approach based on the principle of time-resolved amplified cryptate emission. The functional sensitivity of the assay is 0.06 ng/mL. All testing was performed according to the manufacturer's specifications.[27] The data for patients for whom serum samples or procalcitonin measurements were not available were excluded from further analysis.

Statistical Analysis

We defined 3 categories for interpretation of procalcitonin values: 0.0 to 0.1 ng/mL, 0.1 to 1.0 ng/mL, and more than 1.0 ng/mL. The cutoff values were selected based on the analytic sensitivity of the assay (0.06 ng/mL) and previously published data.[28-30] For the purpose of graphic display, the log method was chosen, and a "zero" procalcitonin value was set to be defined as 0.0001. Other clinical and laboratory parameters, eg, WBC count, were interpreted according to the standard and accepted SIRS criteria and categories.[31] Categorical analysis (Fisher exact test) and continuous analysis (Wilcoxon signed rank test) were performed using the DiagnosisMed library for the R statistical package.[32] The gold standard was defined as a BC result positive for a pathogen, excluding organisms commonly considered BC contaminants (eg, coagulase-negative staphylococci, aerobic and anaerobic diphtheroids, *Micrococcus* sp, *Bacillus* sp). Cultures positive for the latter organisms were considered as false-positives or "negative" for the purposes of statistical analysis.[26] The optimal procalcitonin cutoff value was identified by maximizing the area under the receiver operating characteristic curve and checked against the optimal cutoff value for minimizing the cost of misclassification, assuming that the cost of misclassifying false-negative results takes on integers from 1 to 50.

Results

A total of 367 patients (average age, 47.7 years; range, 18-94 years) were enrolled; the data for 72 patients (average age, 47.9 years; range, 22-94 years) were excluded from further analysis because a serum sample, collected within 24 hours of the BC, was not available for procalcitonin analysis. The demographic data for these patients and the percentage in distribution of BC results (positive-pathogen, positive-contaminant, negative) did not differ in comparison with those

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for all patients whose data were included in the analysis for whom procalcitonin and BC results were available.

The remaining 295 patients (average age, 47.5 years; range, 18-92 years) were classified according to the presence or absence of pathogenic organisms isolated in BCs and the level of procalcitonin detected in their serum samples **Table 1**. Statistically significant differences for procalcitonin levels in relation to patients' BC results were observed ($P = .0004$); results are shown in **Figure 1**. Differences for procalcitonin values were statistically significant between patients with BCs positive for pathogens and patients with negative BCs ($P = .00007$) and for procalcitonin levels for patients with BCs positive for pathogens compared with patients with BCs positive for contaminants ($P = .01$). Procalcitonin levels did not differ between patients with negative BCs and patients with BCs positive for contaminants ($P = .39$).

When comparing clinical criteria for SIRS and procalcitonin results, we did not find any statistically significant correlation, irrespective of the number of SIRS criteria present in individual patients with positive or negative BC results **Figure 2**. Median procalcitonin levels did not differ between patients who had 0 or 1 SIRS criteria and patients who had 2 or 3 SIRS criteria ($P = .66$). Likewise, no significant difference was seen between patients with 0, 1, or 2 SIRS criteria compared with patients who had 3 SIRS criteria ($P = .21$). We also compared the presence of SIRS criteria in patients for whom procalcitonin values were available with SIRS criteria present in patients for whom no procalcitonin values were measured. Again, no statistically significant differences were observed.

Table 1
Procalcitonin and Blood Culture Results in 367 Emergency Department Patients With Presumed Bacteremia or Sepsis

	Blood Culture Results*			
Procalcitonin	Negative	Positive With Contaminant	Positive With Pathogen	Total
Level (ng/mL)				
<0.1	186	11	4	201
0.1-1.0	56	6	6	68
>1.0	19	1	6	26
Analyzed	261	18	16	295
Not analyzed	65	4	3	72
Total	326	22	19	367

* Blood culture results were classified as negative (if no organism was isolated after routine 5-day incubation), positive with contaminant when organisms were identified that were considered common blood culture contaminants as previously defined,[26] and positive with pathogen, when organisms were identified. A statistically significant difference ($P = .0001$) was observed for procalcitonin (PCT) levels according to patients' blood culture results. The proportion of blood culture result type (contaminant vs pathogen) did not differ between patients with PCT results and patients with missing PCT results.

The results of the procalcitonin test properties are illustrated in **Figure 3**. The procalcitonin cutoff value that maximizes the area under the receiver operating characteristic curve (AUC), relative to the gold standard of a BC positive for a pathogen, has been identified as 0.1475 ng/mL. At this level, the following statistical parameters were calculated: sensitivity, 75%; specificity, 78.9%; positive predictive value (PPV),

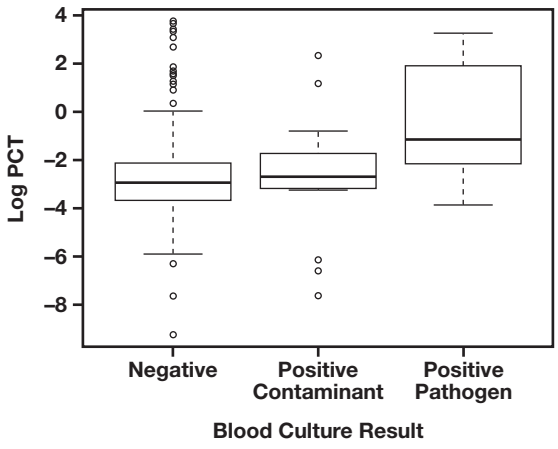

Figure 1 R box plot function ("box and whiskers" plot) for log procalcitonin (PCT) stratified by blood culture results (categorical interpretation). The boxes extend from the 25th to the 75th percentile, with whiskers extending to the most extreme data points (≤1.5 times of the interquartile range from the box). Bold lines indicate the median. Open circles indicate data points that fall beyond the whisker limits.

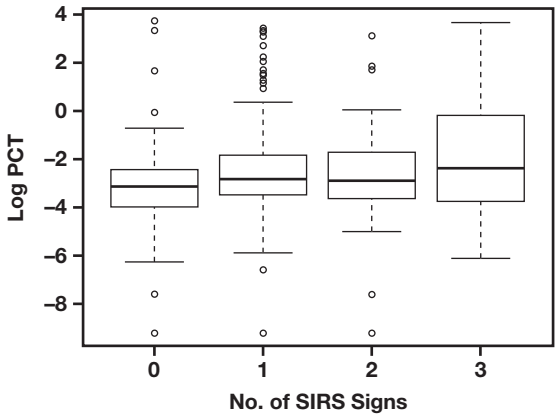

Figure 2 R box plot function ("box and whiskers" plot) for log procalcitonin (PCT) stratified by systemic inflammatory response syndrome (SIRS) criteria. The boxes extend from the 25th to the 75th percentile, with whiskers extending to the most extreme data points (≤1.5 times of the interquartile range from the box). Bold lines indicate the median. Open circles indicate data points that fall beyond the whisker limits. For analysis in this study, we considered the following SIRS criteria: body temperature, ≥38°C or ≤36°C; WBC count, ≥12,000/μL (12.0×10^9/L) or ≤4,000/μL (4.0×10^9/L); heart rate ≥90 beats per minute; and/or systolic blood pressure <90 mm Hg.

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16.9%; negative predictive value (NPV), 98.2%; AUC, 0.79; and accuracy, 78.6%. With a threshold for the cutoff value of procalcitonin of 1.0 ng/mL in relation to positive BC results, the sensitivity was 37.5%, specificity was 92.8%, PPV was 23.1%, NPV was 96.3%, AUC was 0.65, and accuracy was 89.8. A threshold of 0.1 ng/mL for procalcitonin in relation to positive BC results resulted in the following statistical calculations: sensitivity, 75%; specificity, 70.6%; PPV, 12.8%; NPV, 96.3%; AUC, 0.73; and accuracy, 70.9%. These results illustrate a strong NPV for procalcitonin as a screening test for the presence of bacteremia in patients admitted to the ED; however, sensitivity and PPV remained low, even when previously described, validated cutoff values were used.

For 30 patients, there were unexpected results for procalcitonin in comparison with BC results **Table 2**. Of the 30 patients, 12 had already received antimicrobial therapy at the time of BC collection. Of the remaining 18 patients, 4 had BC results positive for a pathogen, but corresponding procalcitonin levels were less than 0.1 ng/mL. In 6 patients, there were positive BCs with a pathogen, but procalcitonin levels were between 0.1 and 1.0 ng/mL. Finally, 8 patients

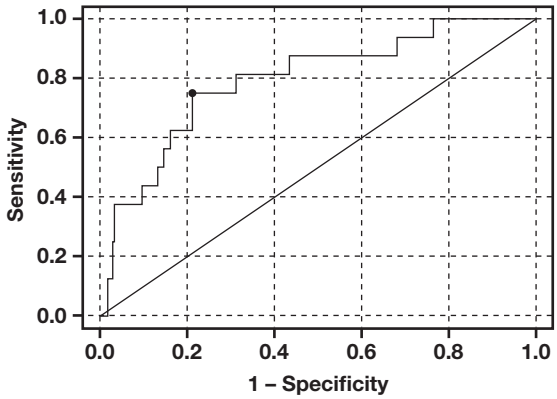

Figure 3 Receiver operating characteristic (ROC) curve for procalcitonin (PCT) test properties and analysis. The PCT cutoff value that maximizes the area under the ROC curve, relative to the "gold standard" of a blood culture positive for a pathogen, is 0.1475 ng/mL. At this cutoff value, the sensitivity is 75%, the specificity is 79.8%, the positive predictive value is 16.9%, the negative predictive value is 98.2%, and the area under the curve is 0.79, with an accuracy of 89.8%.

Table 2
Clinical and Laboratory Data for Patients With Positive and/or Negative Blood Culture Results With Apparent Discrepant Results for PCT Analysis

BC Result/Study ID	PCT (ng/mL)	WBC, /μL (× 10^9/L)	Antibiotic Use at Time of BC Collection	Symptoms and Diagnosis on Admission to ED and Underlying Clinical Conditions	Organism Isolated in BC
Negative with PCT ≥1.0 ng/mL*					
08-53	30.274	13,610 (13.6)	No	ESRD, hemodialysis; PE; TIA	—
08-87	1.419	5,250 (5.3)	No	ESRD, hemodialysis; HTN; gastroenteritis	—
08-106	3.194	25,080 (25.1)	No	ESRD, hemodialysis; chronic wound infection and I&D	—
08-123	2.673	14,510 (14.5)	No	ESRD, hemodialysis; recurrent UTI	—
08-228	2.478	8,220 (8.2)	No	ESRD, hemodialysis; HTN; HIV; DM	—
08-289	37.98	580 (0.6)	No	ESRD, hemodialysis; hepatitis B; COPD; scheduled for lung transplant	—
08-400	27.278	8,940 (8.9)	No	ESRD, hemodialysis; DM; recent glomerulonephritis	—
08-405	21.851	18,960 (19.0)	No	ESRD, hemodialysis	—
Positive with PCT <0.1 ng/mL					
08-83	0.034	7,960 (8.0)	No	Septic arthritis, left ankle	*Staphylococcus aureus*
08-125	0.022	2,850 (2.9)	No	Rash; fever; vomiting	*Gemella morbillorum*
08-131	0.093	11,750 (11.8)	Yes	Recent ureteroplasty; now acute febrile illness	*G morbillorum; Peptostreptococcus* sp
08-489	0.064	10,900 (10.9)	Yes	Left thigh abscess; previous and concurrent antibiotic treatment for SSTI	MRSA
Positive with PCT ≥0.1 and <1.0 ng/mL					
08-156	0.785	25,190 (25.2)	No	Community-acquired pneumonia	*Streptococcus pneumoniae*
08-158	0.223	10,860 (10.9)	No	UTI	*Escherichia coli*
08-234	0.342	24,700 (24.7)	No	HTN; CAD; chronic renal failure; hemodialysis	*S aureus*
08-302	0.157	5,580 (5.6)	Yes	UTI and gastroenteritis after vacation in tropical country	*Salmonella* sp
08-332	0.292	12,880 (12.9)	No	Chronic, complicated UTI	*E coli*
08-343	0.148	7,370 (7.4)	No	Long-term prednisone use; multiple sclerosis	MRSA

BC, blood culture; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; ED, emergency department; ESRD, end-stage renal disease; HTN, arterial hypertension; I&D, incision and drainage; MRSA, methicillin-resistant *S aureus*; PCT, procalcitonin; PE, pulmonary embolism; SSTI, skin and soft tissue infection; TIA, transient ischemic attack; UTI, urinary tract infection.

* 11 patients with negative BCs and 1 patient with BC positive for contaminant organism: all 12 patients received concurrent antibiotic treatment at the time of BC collection; data not shown.

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had procalcitonin values greater than 1.0 ng/mL, but their corresponding BCs were negative for growth. In these 8 patients, various clinical conditions (ie, inflammatory diseases or infections other than BSI) were identified that could explain increased levels of procalcitonin. In addition, all 8 patients in this group had a history of end-stage renal disease and hemodialysis.

Discussion

Rapid detection of bacteremia facilitates early implementation of therapy and identifies patients at high risk for complications.[33,34] Previous studies demonstrated that various clinical markers have poor sensitivity and specificity for predicting early bacteremia in febrile patients.[12-16,33] Similarly, ruling out bacterial sepsis in febrile patients has substantial benefits, including reduction of hospitalization and antimicrobial use and facilitating clinician focus on alternative diagnostic pathways.[34-36] In the present study, we found that procalcitonin is a promising candidate marker for rapid detection of BSI.

In this study of patients recruited from the ED setting, using BC result as the gold standard, we found that procalcitonin levels are dramatically different in patients with and without bacteremia, consistent with previous reports.[20,21,34,35] Previous studies have investigated the usefulness of using procalcitonin as a positive predictive marker for BSI or sepsis with varying outcomes regarding its clinical suitability.[37-39] In patients without bacteremia or systemic infections, procalcitonin levels are 0.1 ng/mL or less.[28-30,40] With less than 0.1 ng/mL used as the cutoff, procalcitonin had a 96.3% NPV for ruling out bacteremia in the ED compared with BC as the gold standard. This high NPV is consistent with previous reports from multiple clinical settings. Liaudat et al[41] studied procalcitonin as an early marker of sepsis in a hospitalized patient population (8% prevalence of bacteremia) and found a high NPV, depending on the cutoff value for the procalcitonin level (99% for 0.2 ng/mL and 95% for 0.5 ng/mL). In a study of 300 hospitalized febrile patients, Bossink et al[14] reported a 90% NPV using a 0.5 ng/mL cutoff value for procalcitonin.

Elevated body temperature above 38.3°C is frequently used as a clinical predictor for bacteremia or sepsis (even though it has poor predictive value and may be a component of many different conditions and diseases).[42-45] Studies have found that the rate of undiagnosed episodes of bacteremia or sepsis in febrile patients ranges from 15% to 50%.[43-45]

Based on the results in this study, we propose that a procalcitonin value of 0.1 ng/mL or less could be used to rule out bacteremia (NPV, 96.3%). We also found a highly significant correlation between procalcitonin levels and positive BC results. Previous studies have demonstrated that procalcitonin levels are correlated with the severity of sepsis and could potentially be used as a prognostic marker in patients with sepsis and severe sepsis.[23,36,37] In our study, we observed differences in the numbers of BC sets turning positive with pathogens. Considering that 4 patients with positive BCs had procalcitonin levels of 0.1 ng/mL or less, we found that in these 4 patients a total of 11 BC sets were collected, yet only 4 sets, 1 for each patient, were positive (36%). The bacteremia in these patients was presumably of low magnitude or even transient, possibly resulting in low procalcitonin levels. On the other hand, in 6 patients with procalcitonin levels of 0.1 to 1.0 ng/mL, a total of 20 BC sets were collected and 9 sets were positive (45%); in patients with procalcitonin levels more than 1.0 ng/mL, 14 (82%) of 17 BC sets collected turned positive. We believe that our results support the previously described correlations of procalcitonin with severity of sepsis. In our study, patients with significant bacteremia and higher procalcitonin levels had significantly more BC sets positive for the pathogen detected, suggesting a more severe form of BSI.

We also observed a significant difference in the length of time to detection (LTD) for positive BCs in relation to procalcitonin levels; in the group of positive BCs with procalcitonin levels less than 0.1 ng/mL, the LTD was on average 57.4 hours, whereas in the group with procalcitonin levels more than 1.0 ng/mL, the mean LTD was 17.0 hours. Studies investigating the impact of LTD and results reporting on length of hospital stay and patient outcome support the importance of shorter LTD to improve patient care.[46] Considering these data and shorter LTDs as an indicator of significant bacteremia, our study demonstrated that all significant BSIs were associated with higher levels of procalcitonin.

These observations help to discriminate between BC contaminants and true pathogens. Depending on country and region, false-positive BCs account for up to 50% of all BCs collected.[47] BCs collected in the ED, which are often performed under suboptimal conditions, are frequently contaminated by common skin flora.[48-50] False-positive BCs result in additional inpatient days, additional clinical evaluations and diagnostic tests, and unnecessary antimicrobial administration. Although algorithms have been proposed during past decades to reduce the burden of false-positive BCs,[26,51,52] a consensus on a gold-standard approach has never been achieved. As such, there is a need for a rapid diagnostic tool to differentiate true-positive from false-positive BCs. In our study, procalcitonin levels in patients with negative BCs and false-positive BCs were similar, and we, therefore, conclude that the procalcitonin level could be used as a rapid tool to rule out bacteremia even in the setting of false-positive BCs. Considering the fact that some studies suggested that the number of BCs positive for the same organism can be used to determine the possibility of BC contamination,[26] we

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believe that procalcitonin results can be used to further support such algorithms.

Because procalcitonin results are available long before BC results, procalcitonin results not only can be an important screening tool to rule out bacteremia but also will further assist in the retrospective assessment of BC results when perhaps only 1 or 2 sets of BCs are positive for organisms known to be potential contaminants. Furthermore, because the test requires only a small amount of serum, it could easily be implemented in the ED as an adjunct laboratory test to distinguish patients with bacteremia from those with a BC positive with a contaminant such as coagulase-negative staphylococci and as a predictor of severity of illness.[53]

As previously shown, many clinical observations, including SIRS criteria, in ED patients have poor predictive values for diagnosing bacteremia and/or sepsis at the bedside.[12,13] The results in our study further support these observations because no statistically significant correlation was seen between procalcitonin values and various combinations of SIRS criteria, while procalcitonin and BC results showed significant correlations with regard to the presence of BSI or sepsis.

Our study has some limitations. The primary aim of this study was to correlate procalcitonin results with BC results, and it included only a limited set of additional clinical data (eg, standard SIRS criteria) in the analysis. Only a limited number of patients with culture-confirmed bacteremia were available for the purpose of this study. As expected, the majority of patients enrolled had negative BCs and were seen in the ED for reasons other than bacteremia or sepsis. We also identified a small subset of patients in our study with markedly elevated procalcitonin levels but negative BC results. It is interesting that all of these patients had a history of end-stage renal disease and hemodialysis but no other commonalities in clinical conditions. Further studies are necessary to better understand the role of procalcitonin as a marker of inflammation in such patient populations because significantly elevated procalcitonin levels in these patients may not consistently be associated with bacteremia and/or sepsis. Considering the performance characteristics of procalcitonin in our study, as well as other previously described studies, it appears to be most reasonable to use the procalcitonin level to rule out bacteremia rather than to predict the presence of a BSI. However, once a procalcitonin value above the defined cutoff has been identified, BCs could be collected in a controlled clinical setting using appropriate skin antisepsis to reduce the risk of contamination. Another factor to consider in our study setup was the possibility of patients receiving antibiotic treatment before BCs were obtained, hence resulting in "false-negative" BC results.

In this retrospective study, procalcitonin seems to be a useful marker to rule out bacteremia in ED patients in our hospital, using a cutoff value of 0.1 ng/mL or less for procalcitonin. BCs may not be necessary in this patient population. A procalcitonin value of 1.0 ng/mL or more was indicative of the presence of bacteremia, and BCs are needed to confirm and identify the presence of bacterial organisms. Additional studies may be necessary to further validate these proposed cutoff values for procalcitonin and the interpretation of procalcitonin values between 0.1 and 1.0 ng/mL. For patients whose procalcitonin values are between 0.1 and 1.0 ng/mL, BCs are still necessary to rule out bacteremia. If further confirmed, procalcitonin could be a very useful and rapid marker in the decision tree to rule out sepsis in ED patients.

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References

1. Angus DC, Linde-Zwirble WT, Lidicker J, et al. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome and associated costs of care. *Crit Care Med.* 2001;29:1303-1310.
2. Martin GS, Mannino DM, Eaton S, et al. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med.* 2003;348:1546-1554.
3. Weinstein MP, Towns ML, Quartey SM, et al. The clinical significance of positive blood cultures in the 1990s: a prospective comprehensive evaluation of the microbiology, epidemiology, and outcome of bacteremia and fungemia in adults. *Clin Infect Dis.* 1997;24:584-602.
4. Wisplinghoff H, Bischoff T, Tallent SM, et al. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. *Clin Infect Dis.* 2004;39:309-317.
5. Friedman G, Silva E, Vincent JL. Has the mortality of septic shock changed in time? *Crit Care Med.* 1998;26:2078-2086.
6. Rivers E, Nguyen B, Havstad S. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med.* 2001;345:1368-1377.
7. Rivers E, Nguyen B, Huang DT. Early goal directed therapy [letter]. *Crit Care Med.* 2004;32:314-315.

DOI: 10.1309/AJCP1MFYINQLECV2

8. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest*. 1992;101:1644-1655.
9. Dellinger RP, Carlet JM, Masur H, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med*. 2004;32:858-873.
10. Harris RL, Musher DM, Bloom K, et al. Manifestations of sepsis. *Arch Intern Med*. 1987;147:1895-1906.
11. Roberts NJ. Impact of temperature elevation on immunologic defenses. *Rev Infect Dis*. 1991;13:462-472.
12. Bates DW, Sands K, Miller E, et al. Predicting bacteremia in patients with sepsis syndrome. *J Infect Dis*. 1997;176:1538-1551.
13. Bossink AW, Groeneveld AB, Hack CE, et al. Prediction of mortality in febrile medical patients: how useful are systemic inflammatory response syndrome and sepsis criteria? *Chest*. 1998;113:1533-1541.
14. Bossink AW, Groeneveld AB, Thijs LG. Prediction of microbial infection and mortality in patients with fever: plasma procalcitonin, neutrophilic elastase-α_1-antitrypsin, and lactoferrin compared with clinical variables. *Clin Infect Dis*. 1999;29:398-407.
15. Jaimes F, Arango C, Ruiz G. et al. Predicting bacteremia at the bedside. *Clin Infect Dis*. 2004;38:357-362.
16. Riedel S, Bourbeau P, Schwartz B, et al. Timing of specimen collection for blood cultures from febrile patients with bacteremia. *J Clin Microbiol*. 2008;46:1381-1385.
17. Fontanarosa PB, Kaeberlein FJ, Gerson LW, et al. Difficulty in predicting bacteremia in elderly emergency patients. *Ann Emerg Med*. 1992;21:842-848.
18. Meisner M. Biomarkers of sepsis: clinically useful? *Curr Opin Crit Care*. 2005;11:473-480.
19. Rangel FM, Pittet D, Costigan M, et al. The natural history of the systemic inflammatory response syndrome (SIRS): a prospective study. *JAMA*. 1995;273:117-123.
20. Assicot M, Gendrel D, Carsin H, et al. High serum procalcitonin concentrations in patients with sepsis and infection. *Lancet*. 1993;341:515-518.
21. Christ-Carin M, Mueller B. Procalcitonin in bacterial infections: hype, hope, more or less? *Swiss Med Wkly*. 2005;135:451-460.
22. Charles PE, Ladoire S, Aho S, et al. Serum procalcitonin elevation in critically ill patients at the onset of bacteremia caused by either gram negative or gram positive bacteria. *BMC Infect Dis*. 2008;8:38. doi:10.1186/1471-2334-8-38.
23. Novotny A, Emmanuel K, Matevossian E, et al. Use of procalcitonin for early prediction of lethal outcome of postoperative sepsis. *Am J Surg*. 2007;194:35-39.
24. Jones AE, Flechtl JF, Brown MD, et al. Procalcitonin test in the diagnosis of bacteremia: a meta-analysis. *Ann Emerg Med*. 2007;50:34-41.
25. Giamarellos-Bourboulis EJ, Giannopoulou P, Grecka P, et al. Should procalcitonin be introduced in the diagnostic criteria for the systemic inflammatory response syndrome and sepsis? *J Crit Care*. 2004;19:152-157.
26. Richter SS, Beekmann SE, Croco JL, et al. Minimizing the workup of blood culture contaminants: implementation and evaluation of a laboratory-based algorithm. *J Clin Microbiol*. 2002;40:2437-2444.
27. BRAHMS USA. BRAHMS PCT sensitive KRYPTOR Instruction Manual (version 4.0us). Annapolis, MD: BRAHMS USA; 2008.
28. Aalto H, Takala A, Kautiainen H, et al. Laboratory markers of systemic inflammation as predictors of bloodstream infection in acutely ill patients admitted to hospital in medical emergency. *Eur J Clin Microbiol Infect Dis*. 2004;23:699-704.
29. Sponholz C, Sakr Y, Reinhart K, et al. Diagnostic value and prognostic implications of serum procalcitonin after cardiac surgery: a systematic review of the literature. *Crit Care*. 2006;10:R145. doi:10.1186/cc5067.
30. Becker KL, Snider R, Nylen ES. Procalcitonin assay in systemic inflammation, infection, and sepsis: clinical utility and limitations. *Crit Care Med*. 2008;36:941-952.
31. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med*. 2008;36:296-327.
32. Brasil P. DiagnosisMed library for the R statistical package. 2009. http://cran.r-project.org/web/packages/DiagnosisMed/index.html. Accessed February 26, 2010.
33. Tokuda Y, Miyasato H, Stein GH. A simple prediction algorithm for bacteremia in patients with acute febrile illness. *Q J Med*. 2005;98:813-820.
34. Heper Y, Akalin EH, Mistik R, et al. Evaluation of C-reactive protein, procalcitonin, tumor necrosis factor alpha, and interleukin-10 levels as diagnostic and prognostic parameters in patients with community-acquired sepsis, severe sepsis, and septic shock. *Eur J Clin Microbiol Infect Dis*. 2006;25:481-491.
35. Vorwerk C, Loryman B, Coats TJ, et al. Prediction of mortality in adult emergency department patients with sepsis. *Emerg Med J*. 2009;26:254-258.
36. Lee CC, Chen SY, Tsai CL, et al. Prognostic value of mortality in emergency department sepsis score, procalcitonin, and C-reactive protein in patients with sepsis at the emergency department. *Shock*. 2008;29:322-327.
37. Peters RP, Twisk WR, van Agtmael MA, et al. The role of procalcitonin in a decision tree for prediction of bloodstream infection in febrile patients. *Clin Microbiol Infect*. 2006;12:1207-1213.
38. Nylen E, Müller B, Becker KL, et al. The future diagnostic role of procalcitonin: the need for improved sensitivity [letter]. *Clin Infect Dis*. 2003;36:823-824.
39. Müller B, Christ-Crain M, Nylen E, et al. Limits to the use of procalcitonin level as a diagnostic marker [letter]. *Clin Infect Dis*. 2004;39:1867-1868.
40. Chirouze C, Schuhmacher H, Rabaud C, et al. Low serum procalcitonin level accurately predicts the absence of bacteremia in adult patients with acute fever. *Clin Infect Dis*. 2002;35:156-161.
41. Liaudat S, Dayer E, Praz G, et al. Usefulness of procalcitonin serum level for the diagnosis of bacteremia. *Eur J Clin Microbiol Infect Dis*. 2001;20:524-527.
42. Knockaert DC, Vanderschueren S, Blockmans S. Fever of unknown origin in adults. *J Intern Med*. 2003;253:263-265.
43. Vanderschueren S, Knockaert D, Adriaenssens T, et al. From prolonged febrile illness to fever of unknown origin: the challenge continues. *Arch Intern Med*. 2003;163:1033-1041.
44. Gaeta GB, Fusco FM, Nardiello S. Fever of unknown origin: a systemic review of the literature for 1995-2004. *Nucl Med Commun*. 2006;27:205-211.
45. Bleeker-Rovers CP, Vos FJ, de Kleijn EM, et al. A prospective multicenter study on fever of unknown origin: the yield of a structured diagnostic protocol. *Medicine (Baltimore)*. 2007;86:26-38.

DOI: 10.1309/AJCP1MFYINQLECV2

46. Beekmann SE, Diekema DJ, Chapin KC, et al. Effects of rapid detection of bloodstream infections on length of hospitalization and hospital charges. *J Clin Microbiol*. 2003;41:3119-3125.
47. Archibald LK, Pallangyo K, Kazembe P, et al. Blood culture contamination in Tanzania, Malawi, and the United States: a microbiological tale of three entities. *J Clin Microbiol*. 2006;44:1425-1429.
48. Bekeris LG, Tworek JA, Walsh MK, et al. Trends in blood culture contamination: a College of American Pathologists Q-Tracks study of 356 institutions. *Arch Pathol Lab Med*. 2005;129:1222-1225.
49. Cockerill FR, Wilson JW, Vetter EA, et al. Optimal testing parameters for blood culture. *Clin Infect Dis*. 2004;38:1724-1730.
50. Gander RM, Byrd L, DeCreszenzo M, et al. Impact of blood cultures drawn by phlebotomy on contamination and health care costs in a hospital emergency department. *J Clin Microbiol*. 2009;47:1021-1024.
51. Kassis C, Rangaraj G, Jiang Y, et al. Differentiating culture samples representing coagulase-negative staphylococcal bacteremia from those representing contamination by use of time-to-positivity and quantitative blood culture methods. *J Clin Microbiol*. 2009;47:3255-3260.
52. Weinstein MP. Blood culture contamination: persisting problems and partial progress. *J Clin Microbiol*. 2003;41:2275-2278.
53. Viallon A, Guyomarc'h S, Marjollet O, et al. Can emergency physicians identify a high mortality subgroup of patients with sepsis: role of procalcitonin. *Eur J Emerg Med*. 2008;15:26-33.

DOI: 10.1309/AJCP1MFYINQLECV2