Persistent Staphylococcus aureus Bacteremia

An Analysis of Risk Factors and Outcomes

Claudia Hawkins, MD; Jenny Huang, ScD; Nancy Jin, MS; Gary A. Noskin, MD; Teresa R. Zembower, MD, MPH; Maureen Bolon, MS, MD

Background: Persistent Staphylococcus aureus bacteremia (pSAB) is an emerging problem among hospitalized patients. We studied key clinical characteristics and outcomes associated with pSAB to better define the epidemiological features of this increasingly recognized clinical entity.

Methods: A retrospective case-control study of patients hospitalized with SAB between January 1, 2001, and September 30, 2004, was conducted to compare the clinical characteristics, management, and outcomes of patients with pSAB (>7 days of bacteremia) with those of a cohort of patients with nonpersistent SAB (<3 days of bacteremia). Patients with 4 to 6 days of bacteremia were excluded from the analysis. To detect a potential association between reduced susceptibility to vancomycin and persistent methicillin-resistant SAB, vancomycin susceptibilities were confirmed using standard dilution methods.

Results: Eighty-four patients with pSAB and 152 patients with nonpersistent SAB were included in the analysis. Methicillin resistance (odds ratio [OR], 5.22; 95% confidence interval [CI], 2.63-10.38), intravascular catheter or other foreign body use (OR, 2.37; 95% CI, 1.11-3.96), chronic renal failure (OR, 2.08; 95% CI, 1.09-3.96), more than 2 sites of infection (OR, 3.31; 95% CI, 1.17-9.38), and infective endocarditis (OR, 10.30; 95% CI, 2.98-35.64) were independently associated with pSAB. The mean time to device removal was significantly longer in patients with pSAB than in patients with nonpersistent SAB (4.94 vs 1.64 days; P < .01). There was no evidence of reduced vancomycin susceptibility among persistent methicillin-resistant S aureus isolates. Clinical outcomes were significantly worse among patients with pSAB.

Conclusions: Many hospitalized patients may be at risk for pSAB. Aggressive attempts to minimize the risk of complications and poor outcomes associated with pSAB, such as early device removal, should be encouraged.

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Rates of Staphylococcus aureus bacteremia (SAB) in hospital and community settings have increased dramatically during the past decade. Persistent SAB (pSAB), commonly defined as bacteremia sustained for 3 days or longer, contributes to many SAB episodes and is increasingly recognized among hospitalized patients.

A more comprehensive analysis is needed to elicit the precise frequency of pSAB and further investigate host characteristics and outcomes associated with this clinical entity. Limitations of the current literature regarding pSAB include variations in study design and study population and definitions of persistence. For example, Fowler and colleagues compared clinical and microbiological characteristics of patients with pSAB and nonpersistent SAB (npSAB) using a definition of persistence of longer than 7 days. Patient numbers in this study were small, and the analysis was limited to patients with methicillin-resistant isolates only. In contrast, in a study by Khatib and coworkers, persistence was defined as longer than 3 days and patients with both methicillin-susceptible S aureus (MSSA) and methicillin-resistant S aureus (MRSA) were included. This observational study included an assessment of risk factors and outcomes associated with pSAB; however, no comparative analysis between the pSAB and npSAB groups was undertaken. Notably, the effects of delayed antibiotic initiation and intravascular device removal on pSAB were not evaluated. Finally, a study by Siegman-Igra and associates focused on the association between vancomycin use and the persistence or recurrence of SAB; further direct comparisons of other host characteristics between patients with pSAB and those with npSAB were not performed.
To understand more about the epidemiological features and outcomes associated with SAB, we performed a case-control study of patients with pSAB and npSAB at our institution. One of the primary aims of our study was to better characterize risk factors associated with pSAB, including those related to patient management, such as the use of vancomycin and intravascular devices. A secondary aim was to study the independent effects of persistent bacteremia and other risk factors on overall mortality in patients with pSAB; to our knowledge, this is something that has not been determined previously.

**METHODS**

This retrospective case-control study was conducted at an 825-bed academic medical center in Chicago. All inpatients with an episode of SAB occurring between January 1, 2001, and September 30, 2004, were identified from the microbiology laboratory database. *Staphylococcus aureus* bacteremia was defined according to the Centers for Disease Control and Prevention criteria.7 Case patients were included in the study if they had an episode of pSAB, defined as bacteremia for longer than 7 days.3 For patients with multiple episodes of pSAB, only the first episode of SAB in each patient was included for analysis. Control patients (1:2 ratio) were selected for inclusion if they had npSAB, which was defined as less than 3 days of bacteremia with documentation of a negative blood culture result within 24 hours of the last positive culture result and no further positive blood culture results during the subsequent 30 days. Patients with intermediate lengths of bacteremia were excluded from the analysis. This was done to ensure a clear distinction between patients with pSAB and patients with npSAB and to reduce the possibility of case and control group misclassification. Patients were also excluded from the analysis if the criteria for true SAB were not met, a follow-up blood culture was not done within 24 hours (for control patients), more than 1 organism was isolated from blood cultures, or the patient was not hospitalized at any time during the episode of SAB.

**MICROBIOLOGICAL IDENTIFICATION AND SUSCEPTIBILITY TESTING OF *S AUREUS* ISOLATES**

The *S aureus* isolates were identified by standard methods.8 Species identification was performed by latex agglutination (Staph aurex Plus; Murex Diagnostics Ltd, Dartford, England). Antimicrobial susceptibility testing was performed using an automated system (Vitek 2; bioMérieux Vitek, Durham, North Carolina) according to Clinical and Laboratory Standards Institute guidelines and the manufacturer’s instructions. In addition, all *S aureus* isolates were inoculated to a brain-heart infusion vancomycin screening agar plate containing 6-µg/mL vancomycin to enhance the sensitivity of detecting strains with reduced vancomycin susceptibility, although no growth occurred at this level. The Clinical and Laboratory Standards Institute vancomycin minimum inhibitory concentration (MIC) break points for *S aureus* used during this study were less than 4 µg (susceptible), 8 to 16 µg (intermediate susceptible), and more than 32 µg (resistant).7 Vancomycin susceptibility testing of MRSA isolates was also performed using the agar dilution method in an attempt to identify isolates with increased MICs within the susceptible range. Agar dilution methods were also performed according to the Clinical and Laboratory Standards Institute procedure outlines.9

**DATA COLLECTION AND DEFINITIONS**

Clinical data collected included baseline demographics, duration of SAB, risk factors for *S aureus*, and route of acquisition of *S aureus*. *Staphylococcus aureus* bacteremia was defined as health care– or community-associated according to standard definitions.10 Additional clinical data collected pertaining to patient management included the presence or absence of a central venous catheter (CVC) or other foreign body (pacemaker, prosthetic joint, or implantable cardiac device) and whether it was considered a definitive site of infection. In addition, data were collected on the status of the CVC or other foreign body during the episode of bacteremia (removed vs retained) and the timing of removal in relation to the onset of bacteremia.

The number of sites of infection (other than bloodstream) was also recorded. Other sites of infection were defined as such if clinical signs were present and *S aureus* was isolated from that site. If bacteremia and systemic signs of infection were present without any obvious source, the site was classified as “unknown.”

Treatment regimens were classified as vancomycin, anti-*staphylococcal* penicillins/first-generation cephalosporins, or other. Antibiotics were considered appropriate if they were active in vitro against the *S aureus* isolate on standard susceptibility testing. The timing of antibiotic initiation was considered appropriate if an antimicrobial agent with activity against the organism was initiated within 48 hours of isolation of the first *S aureus* isolate.

Outcome data collected included duration of hospitalization, the presence of sepsis,11 and death during hospitalization. Sepsis was defined as an outcome if it occurred anytime during the bacteremic episode. Attributable mortality was defined as death with a positive blood culture result or persistent sepsis in the absence of another cause.

**STATISTICAL ANALYSIS**

All statistical analyses were performed using SAS statistical software, version 9.1 (SAS Institute Inc, Cary, North Carolina). The Cochran-Armitage test for trend was used to evaluate the change in the annual episodes of pSAB and persistent MRSA bacteremia (pMRSA) during the study period. Comparisons between patients with pSAB and those with npSAB were performed using the t test for continuous variables and the χ² or Fisher exact test for categorical variables. A univariate analysis of risk factors associated with in-hospital crude mortality in all patients was also performed. Logistic regression was used to assess risk factors associated with pSAB and in-hospital crude mortality. The multiple logistic regression model included all variables significant at the less than .10 level in the univariate model and those variables of clinical importance. The final model was constructed using the stepwise selection procedure. All tests were 2-sided, with the significance level set at .05.

**RESULTS**

From January 1, 2001, to September 30, 2004, there were 1028 episodes of SAB. The proportion of pSAB episodes per year ranged from 8% to 10% and did not change significantly during the study period (P = .47). Methicillin resistance among isolates responsible for pSAB was also stable during the study period (P = .97).
STUDY POPULATION

Of 99 episodes of pSAB, 84 were included in the analysis; of these 84 episodes, 62 (73.8%) were methicillin resistant. Fifteen episodes were excluded from the analysis for the following reasons: medical records not available (n = 10) or recurrent episode (n = 5). A total of 152 patients with npSAB (58 [38.2%] MRSA) were randomly selected as controls.

RISK FACTORS ASSOCIATED WITH pSAB

A univariate analysis of risk factors associated with pSAB is presented in Table 1. Patients with pSAB were significantly more likely to have acquired their infection in a health care setting, have a methicillin-resistant isolate, have had a recent procedure performed, and have underlying diabetes mellitus or chronic renal failure. They were significantly more likely to have a CVC or other foreign body present at the onset of bacteremia and more likely to have the CVC or other foreign body confirmed as a source of infection. When the analysis was restricted to patients with only intravascular devices, no significant differences in the presence of intravascular device at the onset of bacteremia were observed between groups (odds ratio [OR], 1.25; 95% confidence interval [CI], 0.70-2.23; P = .43); however, patients with pSAB were significantly more likely to have an intravascular device that was confirmed as a source of infection (OR, 1.90; 95% CI, 1.01-3.59; P = .03). Patients with pSAB were more likely to have multiple sites of infection and to have endocarditis. Patients with pSAB were no more likely to have had a recent S aureus infection or to have received recent antibiotics or corticosteroids than patients with npSAB. Rates of malignancy did not differ significantly (OR, 0.65; 95% CI, 0.33-1.27) between cases and controls.

Results of the multivariate analysis indicate that independent risk factors associated with pSAB included methicillin resistance (OR, 5.22; 95% CI, 2.63-10.38; P ≤ .01), presence of a CVC or other foreign body before the bacteremic episode (OR, 2.37; 95% CI, 1.11-5.06; P = .03), chronic renal failure (including patients undergoing hemodialysis) (OR, 2.08; 95% CI, 1.09-3.96; P = .03), multiple sites of infection (OR, 3.31; 95% CI, 1.17-9.38; P = .02), and endocarditis (OR, 10.30; 95% CI, 2.98-35.64; P ≤ .01), as defined by the modified Duke criteria.13

CLINICAL MANAGEMENT AND OUTCOMES OF PATIENTS WITH pSAB

A univariate analysis of clinical management and outcomes associated with pSAB is shown in Table 2. Removal rates of CVCs or other foreign bodies did not significantly differ between patients with pSAB and patients with npSAB. However, there were significantly longer de-
lays in the removal of CVCs and other foreign bodies among patients with pSAB. Similar observations were made after the analysis was restricted to patients with intravascular devices alone (data not shown). The time to initiation of appropriate antibiotics was slightly longer, although not statistically significant, in patients with pSAB vs patients with npSAB. Patients with pSAB were more likely to receive appropriate initial antibiotics. The initial use of vancomycin did not differ significantly between patients with pSAB and patients with npSAB. The initiation of additional antibiotics with synergistic anti-staphylococcal activity was more frequent among patients with pSAB. β-Lactam initiation within 72 hours was not significantly different between the subset of patients with persistent MSSA bacteremia (MSSAB) and those with nonpersistent MSSAB. The proportion of patients who received vancomycin for 7 days or longer was significantly higher among those with nonpersistent MSSAB than those with persistent MSSAB.

Patients with pSAB had significantly worse outcomes than patients with npSAB, including in-hospital crude mortality, duration of hospitalization, and sepsis. Attributable mortality in patients with pSAB was 19.0%, which was significantly higher than that of patients with npSAB (Table 2).

RISK FACTORS FOR IN-HOSPITAL CRUDE MORTALITY

To evaluate whether pSAB was independently associated with in-hospital mortality, we performed a univariate analysis of baseline risk factors associated with death, including persistent and nonpersistent status (Table 3). In a multivariate analysis of risk factors (including variables at the <.10 significance level), only sepsis (OR, 10.00; 95% CI, 4.75-25.27; P < .01) and malignancy (OR, 2.82; 95% CI, 1.12-7.09; P < .03) were independent predictors of in-hospital crude mortality. Neither persistent status (OR, 1.82; 95% CI, 0.77-4.28; P = .17) nor methicillin resistance (OR, 1.14; 95% CI, 0.48-2.73; P = .76) was an independent predictor of in-hospital crude mortality.

VANCOMYCIN SUSCEPTIBILITIES AMONG pMRSA AND NONPERSISTENT MRSA ISOLATES

The MIC (measured in micrograms per milliliter) determination using the agar dilution method was performed on 112 of 120 MRSA isolates (59 of 62 [95.2%] of pMRSA isolates and 53 of 58 [91.4%] of nonpersistent MRSA [npMRSA] isolates). Three isolates from patients with pMRSA and 5 isolates from patients with nonpersistent MRSA (npMRSA) were unavailable for testing. Most isolates (56 of 59 pMRSA and 49 of 53 npMRSA isolates) had an MIC of 1 µg/mL, and there was no evidence of increasing MICs among pMRSA isolates. Both of the isolates with an MIC of less than 2 µg/mL were from patients with npMRSA.

COMMENT

This large case-control study contributes new findings to the existing literature on pSAB. In addition to identi-
fying a number of unique risk factors associated with pSAB, we characterized the local trends among pSAB and npMRSAB, which, contrary to initial perceptions, remained stable during the study period. We were also able to confirm the high rate of morbidity and mortality associated with this clinical syndrome.

Issues related to patient management of pSAB, in particular, antibiotic use and device removal, have been mostly neglected in prior studies. In the present study, we demonstrated significantly higher rates of CVC or intravascular devices alone. A similar observation was made by Fowler et al3; however, the finding failed to achieve statistical significance.

Other notable findings in the management of patients with pSAB concerned antibiotic use. In our study, a trend toward a longer time to appropriate antibiotic initiation was noted among patients with pSAB than in patients with npSAB, although the proportion receiving appropriate initial antibiotics was higher among those with pSAB. In the only other study, to our knowledge, to examine antibiotic timing and its effect on persistent bacteremia, no significant difference was found in the time to removal, which was significantly higher among patients with pSAB. This factor has important implications given the increasing prevalence of implanted medical devices. An important finding regarding the management of foreign bodies was the disparity in time to removal, which was significantly longer in patients with pSAB. A significant difference remained when restricting the analysis to patients with intravascular devices alone. A similar observation was made by Fowler et al3; however, the finding failed to achieve statistical significance.

We did not detect an association between vancomycin use and pSAB in our study. This is in contrast to 2 other studies2,6 that found vancomycin use to be independently associated with pSAB. Several researchers15,16 have demonstrated delayed clearance of MSSAB when vancomycin is used as initial therapy, which could potentially explain associations observed between vancomycin use and pSAB in studies that included patients with MSSAB. To test this hypothesis further, we compared the proportion of patients with MSSAB who continued to receive vancomycin therapy for longer than 7 days between our 2 study groups. Interestingly, significantly fewer patients with persistent MSSAB who continued to receive vancomycin for longer than 7 days vs those with nonpersistent MSSAB. We also examined the frequency of β-lactam initiation within 72 hours in patients with MSSAB who initially received vancomycin. More patients with persistent MSSAB switched to a β-lactam within 72 hours; however, the difference was not significant. The lack of significant findings regarding the impact of vancomycin on outcome in our study was likely because of the fact that most of the isolates were MRSA (particularly among individuals with pSAB) and that vancomycin was the initial treatment in most patients with methicillin-resistant and methicillin-sensitive pSAB and npSAB. In addition, surprisingly few patients with MSSAB who were treated initially with vancomycin received β-lactam therapy thereafter.

Reduced susceptibility to vancomycin among MRSA isolates may also be contributing to the development of pSAB.9,17 Heteroresistance among susceptible strains of S aureus, S aureus isolates with reduced vancomycin susceptibilities, and the phenomenon of MIC creep (increasing MICs within the susceptible range among MRSA isolates) have been shown to be associated with failure of vancomycin therapy and episodes of pSAB.18-20 We performed additional vancomycin susceptibility testing using the agar dilution method among isolates from patients
with pMRSAB and npMRSAB to determine whether MIC creep was present among our MRSA isolates. No evidence of MIC creep was uncovered. Vancomycin MICs determined using standard disk diffusion tests, dilution methods, or rapid, automated, commercial systems (Vitek 2 or MicroScan WalkAway; Dade Behring Inc, West Sacramento, California) have failed to differentiate between MRSA strains, susceptible strains of S aureus with heteroresistance, and S aureus isolates with reduced vancomycin susceptibilities at the current break point of greater than 4.22 Determination of vancomycin bactericidal activity through a minimum bactericidal concentration, serum bactericidal assay, or kill curves may have been a more sensitive means to uncover emerging resistance among our MRSA isolates. An additional finding was that there was minimal interindividual MIC variation among the isolates using the agar dilution method. However, the MICs were categorically consistent with those obtained using the automated system (Vitek 2).

Other noteworthy findings in our study concerned outcomes in patients with pSAB. High rates of morbidity and mortality among patients with pSAB were observed, exceeding rates observed in other studies.24 Patients with pSAB had significantly longer hospitalizations, higher attributable and crude mortality rates, and higher rates of sepsis. When we performed further analyses of outcomes to look for the independent effects of pSAB and other potential risk factors on all-cause mortality, 2 findings were notable. First, no significant association between MRSA and all-cause mortality was observed. This finding contrasts to those in other studies in which persistence itself was associated with mortality in other studies.23 Determination of vancomycin bactericidal activity through a minimum bactericidal concentration, serum bactericidal assay, or kill curves may have been a more sensitive means to uncover emerging resistance among our MRSA isolates. An additional finding was that there was minimal interindividual MIC variation among the isolates using the agar dilution method. However, the MICs were categorically consistent with those obtained using the automated system (Vitek 2).

In summary, many hospitalized individuals with SAB are at risk for persistent bacteremia, particularly those with CVCs or other foreign bodies, methicillin-resistant isolates, and chronic renal failure. Rates of pSAB are expected to increase as populations at risk expand. Aggressive attempts to minimize the risk of complications associated with pSAB should be encouraged, especially in view of the high rate of morbidity and mortality associated with this clinical entity. This may include a more thorough diagnostic assessment of patients with pSAB for multiple sites of infection and timely removal of CVCs and other devices.

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Correspondence: Claudia Hawkins, MD, Department of Infectious Diseases, Northwestern University Feinberg School of Medicine, 676 N St Clair, Ste 200, Chicago, IL 60611 (c-hawkins@md.northwestern.edu).

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