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Original Communication

Incidence and risk factors for persistent *Staphylococcus aureus* bacteremia

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ABSTRACT

Persistent *Staphylococcus aureus* bacteremia (SAB) has been documented throughout the literature, with rates of approximately 5-20%. Limitations of these reports include inconsistent definitions, lack of consideration for appropriate therapy, and small patient populations. Patients who developed SAB between July 1st, 2008 and June 30th, 2011 were examined in a retrospective cohort analysis to compare persistent (≥ 48 hours of active therapy) SAB to non-persistent (< 48 hours of active therapy) SAB. 366 cases of SAB were identified over the 3-year study period. 39 cases were persistent by definition (10.7%). Both severe renal impairment and renal replacement therapy were significantly associated with persistent SAB. The presence of osteomyelitis or central venous access device was significantly associated with persistent SAB. Median length of hospital stay was 18 days in the persistent group and 11 days in the non-persistent group ($p = 0.0082$). Mortality rate during hospitalization was not significantly different between the two groups; 15% in the persistent cohort versus 7.5% in the non-persistent cohort ($p = 0.311$). Persistent SAB was associated with a variety of risk factors and significantly increased length of hospital stay. There was also a trend toward higher mortality rate in patients with persistent bacteremia.

KEYWORDS: *Staphylococcus aureus*, bacteremia, persistence, prevalence, risk-factors

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INTRODUCTION

Persistent bacteremia from *Staphylococcus aureus* is a common problem despite treatment with anti-staphylococcal therapy. In a multicenter study, out of 448 cases of *Staphylococcus aureus* bacteremia (SAB), 171 met criteria for SAB without endocarditis, and received treatment with nafcillin or vancomycin for at least 10 days within 14 days following the first positive blood culture. About half (49%) of the SABs were caused by methicillin-resistant *Staphylococcus aureus* (MRSA). Persistent bacteremia for more than 3 days was observed for methicillin-susceptible *Staphylococcus aureus* (MSSA) in 1 of 18 (5.6%) receiving nafcillin and 15 of 70 (21%) receiving vancomycin. SAB had cleared by day 7 in patients with MSSA bacteremia treated with nafcillin but remained present in 5 of 83 (6.0%) and 4 of 83 (4.8%) at 3 days and 7 days, respectively for patients with MRSA [1].

In a prospective, observational study of consecutive SAB cases without regard to therapy timing, 38.4% of 245 patients developed persistent bacteremia defined as positive cultures for at least 3 days. Cox regression analysis identified associated risk factors as endovascular source, vancomycin treatment, cardiovascular prosthesis, metastatic infection, and diabetes [2]. The same authors performed a follow-up study with persistence defined as positive culture for at least 7 days after the initial positive culture. Based on this more stringent definition, 11.0% of the original 245 patients had persistent bacteremia, and 15.1% of the new study population met criteria for persistent bacteremia. Logistic regression analysis identified associated risk factors as endovascular

source, vancomycin treatment, metastatic infection, and diabetes [2, 3]. The focus of another report was MRSA in the intensive care unit. The study site had 1125 cases of SAB of which 204 (18%) were MRSA and 21 (1.9%) were MRSA from the intensive care unit. A sample of 60 patients with MSSA bacteremia while in the intensive care unit was selected for a control group. Persistent SAB was observed in 7 (33%) with MRSA and 4 (6.7%) patients with MSSA infection; however, all of the MRSA patients were treated with an inappropriate drug initially, and bacteremia cleared after glycopeptide therapy was initiated. The median duration of bacteremia was 5.3 days for MRSA and 1.4 days for MSSA. This study demonstrates the importance of considering persistence of bacteremia in relation to timing of appropriate antimicrobial treatment [4].

A retrospective case-control study examining risk factors and outcomes of persistent SAB (≥ 7 days of bacteremia) compared to non-persistent SAB (≤ 3 days of bacteremia) found that MRSA was significantly more likely than MSSA to cause persistent bacteremia. Other risk factors associated with persistent SAB included: intravascular catheters, presence of foreign body, chronic renal failure, more than 2 sites of infection, and infective endocarditis. The authors excluded all patients with bacteremia persisting between 4 to 6 days in order to ensure a clear distinction between the two groups [5].

The relationship between poor outcomes and persistent SAB is well established. Complicated SAB is defined by positive follow-up blood culture at 48-96 h, community-acquired infection, persistent fever at 72 h, and skin lesions suggestive of acute systemic infection [6]. A prospective, observational study at six university teaching hospitals identified 505 consecutive patients with SAB and persistent bacteremia (positive blood cultures on day 3 of appropriate antibiotic therapy) was an independent risk factor for endocarditis and mortality [7]. Several studies have demonstrated that persistent SAB at 24 to 96 h after initiation of treatment was associated with increased risk of endocarditis and other complications including metastatic infection at a distant focus, anatomically unrelated to the source infection site [8, 9, 10]. Interestingly, persistent SAB was not associated with bone and joint infections [10]. Based on a broad definition of complicated SAB, the single most important risk factor was persistent SAB [11].

This study was performed to characterize the frequency of persistent SAB and to examine risk factors for persistence. One significant difference from earlier studies is that this study focuses on duration of positive cultures after receipt of appropriate anti-staphylococcal therapy which is similar to studies aimed at determining complications of SAB.

METHODS

This retrospective, single center study at a tertiary acute care hospital evaluated a cohort of patients with and without persistent SAB. Subjects must have had SAB over a 3-year period. Potential subjects were identified by ICD-9 code for SAB and/or at least one positive blood culture for *Staphylococcus aureus*. Exclusion criteria included death within 48 hours of index blood culture (defined below), age < 2 years, pregnant or breast-feeding women, or an initial positive blood culture before the 3-year inclusion period.

The number of cases without persistent SAB was expected to be much larger than the number of cases defined as having persistent SAB. Patients with SAB were listed in chronological order by index culture date and time. The patients' medical records were screened for inclusion criteria and all cases that met criteria for the persistent SAB group were enrolled. In an attempt to keep an approximately equal group size and create a patient population that was similar between the two groups with a focus on the persistent SAB group, a 5×5 blocking scheme was used. For every five patients in persistent SAB group, the first five patients with non-persistent SAB in the same time period were selected and enrolled. This process was repeated in multiples of five until the entire study population was selected. "Skipped" patients in the non-persistent SAB group were only included to determine the overall frequency of persistent SAB and were not included for the detailed data collection.

Onset of SAB was defined as the date and time when the first positive blood culture with *Staphylococcus aureus* isolated was obtained and deemed the index blood culture (Day 0). Persistent SAB was defined as any case with positive blood cultures collected at least 48 hours after initiation of an active antibiotic therapy. Non-persistent SAB was defined as any case with positive blood cultures for less than 48 hours after initiation of active therapy. For MSSA isolates, appropriate therapy included cefazolin, nafcillin, daptomycin, vancomycin, or

linezolid. For MRSA isolates, active therapy included vancomycin, daptomycin, or linezolid.

Baseline characteristics and demographic data including age, sex, weight, height, race, admitting diagnosis, and prior exposure to healthcare settings were collected. Creatinine clearance was estimated using the Cockcroft and Gault equation with severe renal impairment defined as creatinine clearance < 20 mL/min or subject on renal replacement therapy. Specific comorbid conditions, immunosuppression, presence of a central venous access device, site(s) of infection, culture and susceptibility data, antimicrobial agents prescribed, response to therapy, and survival to discharge were recorded.

Statistical analysis was performed using SAS (Statistical Analysis System, version 9.3, SAS institute Inc. Cary, NC). Demographic information and baseline patient characteristics were evaluated using descriptive statistics. Continuous variables were evaluated using the student's t-test or Wilcoxon signed rank test and categorical variables were evaluated with logistic regression or Fisher's exact test. The *a priori* alpha level was 0.05 for all analyses.

RESULTS

A total of 366 cases and 990 separate blood cultures were screened for inclusion and exclusion criteria. Ninety-three cases identified by outpatient blood cultures were never admitted to this hospital. We excluded 145 patients including 121 who had an ICD-9 code for SAB, but no documented SAB; 6 patients who had initial blood cultures with *Staphylococcus aureus* isolated outside of the inclusion dates; and 18 patients with early mortality or age < 2 years. The dataset used for incidence of persistent SAB included 221 separate admissions, 834 separate blood cultures, and 366 episodes of SAB. Of this group, 39 episodes were found to have persistent SAB (10.7%) and 327 were found to have non-persistent SAB. The detailed analysis dataset included 79 episodes of SAB with 39 episodes of persistent SAB and 40 episodes of non-persistent SAB.

Patients were similar with respect to demographics and other baseline characteristics (Table 1). There were 44 cases (55.7%) involving MRSA and 35 cases (44.3%) involving MSSA. The rate of persistence in the study population was 59.1% for MRSA and 37.1% for MSSA (p = 0.053). Table 2 provides selected comorbid conditions and associated risk of persistent SAB. Several metrics of renal disease were explored as risk factors; however, the strongest risk factor was severe renal disease, followed by diabetes mellitus. Only renal disease (severe renal disease or renal replacement therapy) was independently associated with risk of persistent SAB on multivariate logistic regression. The data available did not allow discrimination between renal replacement therapy and severe renal disease; however, renal replacement therapy appeared to be a very important risk.

Two infection sites were independently associated with persistent SAB including osteomyelitis and central venous access devices as shown in Table 3. Based on univariate analysis, abscess was associated

Table 1. Demographic data for persistent and non-persistent *Staphylococcus aureus* bacteremia patient populations.

	Persistent (N = 39)	**Non-persistent (N = 40)**	**p-value**
Age in years, Mean (± SD)	53.4 ± 16.7	54.0 ± 19.1	0.88
Male sex, N (%)	25 (64)	25 (63)	0.88
Race/Ethnicity, N (%) White, non-Hispanic White, Hispanic African American Asian, Pacific Islander Other	 25 (64) 7 (18) 3 (7.7) 1 (2.6) 3 (7.7)	 21 (53) 10 (25) 3 (7.5) 1 (2.5) 5 (13)	0.92
Prior exposure to healthcare (past 12 weeks), N (%)	30 (77)	25 (63)	0.16
Prior antibiotic exposure (past 30 days), N (%)	11 (28)	13 (33)	0.68

Table 2. Association of comorbid conditions with risk of persistent *Staphylococcus aureus* bacteremia.

Medical condition	Persistent (N = 39)	Non-persistent (N = 40)	OR (95% CI)
Severity of renal disease			
Moderate	4 (10.3)	7 (17.5)	0.914 (0.228–3.66)
Severe	20 (51.3)	9 (22.5)	3.556 (1.29–9.83)
Acute kidney Injury	16 (41)	10 (25)	2.09 (0.800–5.44)
Chronic renal disease			
CLcr < 20 ml/min or renal replacement therapy	4 (17.4)	2 (6.67)	3.20 (0.521–19.7)
CLcr 20-39.9 ml/min	2 (8.7)	1 (3.33)	3.20 (0.266–38.4)
CLcr 40-59.9 ml/min	2 (8.7)	3 (10.0)	1.07 (0.159–7.15)
Any renal replacement therapy	14 (36)	5 (13)	3.92 (1.25–12.3)
Chronic liver disease	7 (18)	6 (15)	1.24 (0.376–4.08)
Diabetes mellitus	17 (44)	9 (23)	2.66 (1.004–7.06)
Immunosuppression	14 (36)	16 (40)	0.84 (0.338–2.09)

CLcr = estimated creatinine clearance
OR = odds ratio

Table 3. Sites of infection for persistent and non-persistent *Staphyloccous aureus* bacteremia patient populations.

Other site of infection, N (%)	Persistent (N = 39)	Non-persistent (N = 40)	OR (95% CI)
Univariate			
Central venous access device	19 (49)	13 (33)	1.97 (0.792–4.91)
Lung	5 (13)	5 (13)	1.03 (0.273–3.88)
Urine	5 (13)	1 (2.5)	5.73 (0.638–51.5)
Skin or skin-structure	7 (18)	9 (23)	0.753 (0.250–2.27)
Abscess	10 (26)	3 (7.5)	4.25 (1.07–16.9)
Pacemaker/Artificial Heart	5 (13)	3 (7.5)	1.81 (0.403–8.17)
Endocarditis	8 (21)	2 (5)	4.90 (0.97–24.8)
Osteomyelitis	11 (28)	2 (5)	7.46 (1.53–36.4)
Septic joint	4 (10)	3 (7.5)	1.41 (0.294–6.75)
Any other site	28 (72)	24 (60)	1.70 (0.662–4.35)
Multivariate			
Osteomyelitis			9.89 (1.93–50.7)
Central venous access device			2.72 (1.02–7.28)

with persistent SAB; however, this fell out on the multivariate analysis because 7 of 13 patients with osteomyelitis also had an abscess. Multivariate analysis also resulted in a stronger association between central access device and persistent SAB. A total of 19 and 13 patients in the persistent and non-persistent group, respectively had a catheter related infection. Another interesting finding was that MRSA accounted

for 73.7% of the SABs in the persistent group and only about half of the SABs in the non-persistent group (p = 0.283). Catheter removal occurred in a median 2.5 (1-12) days in the persistent group and 4.0 (1-36) days in the non-persistent group (p = 0.181). In addition, endocarditis showed a borderline risk; however, this is probably due to the small number of cases and type 2 error. The planned data collection did not allow determination of whether site of infection was a risk factor for persistent SAB or vice versa.

Among patients with non-persistent SAB, 10 (25%) did not have a documented negative culture prior to discharge. Most of these episodes had only the index positive culture reported and there were no further blood cultures collected prior to discharge. Of the three patients who died prior to discharge, one died within two days of the index culture and one died after 47 days. In the latter case, cultures were intermittently positive for MRSA over that entire time period. The third patient died about 3 weeks after documented clearance of MSSA bacteremia.

Among patients with persistent SAB, two died prior to discharge with preceding positive blood cultures. There were six patients discharged without evidence of blood culture clearance despite persistently positive blood cultures after 3 to 16 days of appropriate therapy. Apparently, the patients were discharged on clinical grounds with plans to follow-up post discharge. However, one of the patients remained in the hospital for 11 more days without obtaining additional blood cultures.

Patients with MSSA bacteremia (n = 37) were generally started on empiric vancomycin initially (n = 35) within a median (range) 8.4 (0-72) hours from the time of index culture collection. Once the organism was designated as MSSA, therapy changed (n = 30) to nafcillin or cefazolin within a median 2.7 (0.38-19) days. The median times to initiation of treatment (p = 0.527) or streamlining (p = 0.621) did not depend on group. For MRSA, patients were generally treated empirically with vancomycin (n = 42) within a median 13 (0-110) hours from the time of index culture collection. In the persistent group (n = 39), the last positive culture was collected after a median (range) 5.7 (2.3-33) days of appropriate therapy. Resolution of SAB was documented in 33 patients after a median 7.1 (2.7 to 42) days of appropriate therapy. Daptomycin was used in 9 patients (2 to 26 days) and linezolid was used in 6 patients (< 1 to 8 days) with persistent SAB due to MRSA. For MSSA persistent SAB, linezolid was used only once for 8 days. Concomitant rifampin therapy was used in 10 patients with persistent SAB compared to 1 patient without persistent SAB. Concomitant gentamicin was used in 3 patients, all with persistent SAB. Clearance of SAB was possible in most of the patients.

There was no difference in relapse (15% versus 5%; p = 0.12) or death (15% versus 7.5%; p = 0.311) between persistent and non-persistent cohorts, respectively as shown in Table 4. However, patients with persistent SAB had a significantly higher median length of hospital stay (18 days versus 11 days; p = 0.0082). The duration of hospitalization was strongly correlated with persistently positive SAB [length of hospital stay post treatment (days) = 2.17 × day of last positive culture + 11.8; p < 0.0001] such that each day of bacteremia correlated with > 2 days of added hospital stay.

Table 4. Outcome data for persistent and non-persistent *Staphylococcus aureus* bacteremia patient populations.

Outcome	**Persistent (N = 39)**	**Non-persistent (N = 40)**	**OR (95% CI) or p-value**
Infection relapse rate, N (%)	6 (15)	2 (5)	3.45 (0.652–18.3)
In hospital mortality rate, N (%)	6 (15)	3 (7.5)	2.24 (0.519–9.69)
Length of stay in days, Median (Range)	18 (4-334)	11 (0-78)	0.0082
Length of stay pre-index culture in days, Median (Range)	0 (0-252)	0 (0-56)	0.796
Length of stay post-index culture in days, Median (Range)	18 (4-198)	8.5 (0-55)	0.0024

DISCUSSION

Overall, persistent SAB occurred in 10.7% of SAB episodes using the definition of at least 48 h of bacteremia after initiating active antibiotic therapy. Previous studies have examined duration of positive blood cultures irrespective of treatment. Even though the number of persistent SAB cases in our study was relatively small (39 cases), it is one of the largest populations identified to directly compare persistent and non-persistent SAB. Khatib *et al.* presented two cohort studies involving a similar number of patients with persistent SAB; however, persistence was defined at positive blood cultures for 7 days [2, 3]. These studies documented a higher frequency (11.0 to 15.1%) of persistent SAB than observed in this study. However, 93 subjects with SAB (outpatient blood culture) were never admitted to this institution, but were counted in the denominator. If these subjects were excluded the frequency of persistent SAB could be as high at 17.6%. The risk factors for persistent SAB included endovascular source, metastatic infection, diabetes, vascular access device, presence of prosthesis, and vancomycin treatment [2, 3]. In our study, diabetes was not independently associated with persistent SAB after taking severe renal disease into account; however, the presence of a vascular access device remained an important risk factor. End stage renal disease in patients on hemodialysis is an established risk for SAB with the highest risk in patients that have a central venous access device in place [12, 13]. One other study demonstrated that having chronic renal failure including undergoing hemodialysis is a risk factor for persistent SAB [5]. Although patients dialyzed with a venous catheter in place are at increased risk for infection-associated mortality, the frequency of manifestation as persistent SAB was not reported [14]. Our results showed an association between osteomyelitis and persistent SAB. Osteomyelitis is most likely a complication of sustained SAB rather than vice versa [15, 16].

Although not directly assessed in our study, patients treated with vancomycin were found to have independent predictors of increased rate of persistence (≥ 7 days after initiation of treatment) compared to non-persistence (≤ 3 days after initiation of treatment). Most of the patients in our study, received empiric vancomycin within hours of collecting the initial blood culture that later became positive for *Staphylococcus aureus*. In the event that the isolate was MSSA, therapy was usually changed to an anti-staphylococcal penicillin or cephalosporin. An association between vancomycin treatment and poor outcome has usually been detected when vancomycin was continued for MSSA [1] or when vancomycin therapy was correlated with isolation of MRSA [2, 3]. In another study, vancomycin MIC of 2 mg/L was associated with persistent SAB and increased infection-related mortality [17].

Our study is limited to one center and is retrospective. The major concern is not having planned follow-up blood cultures. Blood cultures may have been positive for at least 48 h in more patients than captured, but were not detected because blood cultures were not obtained with consistent timing. In the planning stage, we elected not to develop specific matching criteria for the control group; however, the two groups were comparable in demographic characteristics. We also could have used all or a larger number of subjects for the non-persistent SAB group. The decision to target equal group size was based on time constraints with the collection of detailed information from medical records. Since there is sparse literature dealing with risk factors for persistent SAB, it would have been difficult to identify *a priori* matching characteristics, and any characteristic selected could influence our ability to identify risk factors from our data. Using our 5×5 blocking scheme, we feel the effects of such a limitation are minimized and should not affect the current results of this study.

This study showed a potential problem with documenting clearance of positive blood cultures in that the last culture obtained in the hospital was positive in about 20% of the patients. Follow-up was not available post-discharge to determine if blood cultures were repeated or ultimate clinical outcome. The median (range) length of hospital stay after appropriate antibiotic treatment was initiated was 13 (0-198) days. The presence of persistent bacteremia should raise concerns of endocarditis or other intravascular infection, and in most cases warrant treatment for a minimum of 4 weeks [18, 19].

CONCLUSION

Persistent SAB defined as positive blood cultures for > 48 h after initiation of appropriate therapy was

noted in 10.7% of patients. Severe renal disease, osteomyelitis and presence of a central venous access device were independently associated with risk of persistent SAB. For each day of persistent SAB, length of hospital stay is prolonged by 2 days on average.

CONFLICT OF INTEREST STATEMENT

The authors have no relevant conflicts of interest to disclose.

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