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ORIGINAL RESEARCH

Staphylococcus aureus Bacteremia (SAB) With Associated *S. aureus* Bacteriuria (SABU) as a Predictor of Complications and Mortality

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BACKGROUND AND OBJECTIVES: *Staphylococcus aureus* (SA) bacteremia (SAB) is associated with a high rate of complications, most of which are related to hematogenous seeding into deep tissues or prosthetic material. SA bacteriuria (SABU) has been described in association with SAB, but has not been evaluated as a predictor for complicated bacteremia, which was the objective of our study.

METHODS (DESIGN, SETTING, AND PATIENTS): We conducted a retrospective study of patients admitted to the hospital with SAB. The 118 patients included in the study were divided in 2 cohorts: a group with SABU and a group without SA in the urine. We followed the 2 cohorts for an average of 8 months and evaluated the differences in complications and mortality.

RESULTS: SABU was found in 28 of 118 patients with SAB. Eighteen patients (64%) in this group had complications from the bacteremia, while in the group without SABU only 33% (30/90 patients) had complications ($P = 0.004$). The SABU group also had more deaths (32% vs. 14%; $P = 0.036$).

CONCLUSIONS: In this population of hospitalized patients with SAB, the presence of SABU was associated with an increased risk of early complications, including septic shock, and with higher mortality. A routine urine culture in search of SABU may be a helpful tool for detection of those patients with SAB who are at increased risk of complications and death. ***Journal of Hospital Medicine*** **2010;5:208–211.** © *2010 Society of Hospital Medicine.*

KEYWORDS: complications from *Staphylococcus aureus* bacteremia, predictor of complications and mortality, *Staphylococcus aureus* bacteremia, *Staphylococcus aureus* bacteriuria.

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Staphylococcus aureus (SA) infection can cause a wide range of clinical syndromes, from folliculitis to life-threatening endocarditis. Further, SA is second only to *S. epidermidis* as a cause of bacteremia in hospitalized patients.[1,2] Recent single-institution studies suggests that SA could be the most frequent cause of nosocomial bacteremia,[3,4] but this needs to be validated in multicenter studies. SA bacteremia (SAB) is often complicated by hematogenous seeding into deep tissues or prosthetic material. The association of future hardware infection following SAB is well documented.[5,6] One study showed that SAB can precede and be associated with prosthetic joint infections in up to 34% of cases.[6] Intravascular cardiac devices can also be infected by SAB, with rates from 28% to 75% depending on how early the bacteremia occurred in relation to the implantation of the device.[5] Risk stratification for these complications is a clinical challenge. Fowler et al.[7] postulated some clinical identifiers of complicated SAB; however, predicting which patients will develop a complication from SAB remains very difficult. Muder et al.[8] demonstrated that the presence of SA bacteriuria (SABU) correlates with subsequent SAB, but a possible association of SABU with complicated bacteremia was not examined. A more recent study from Huggan et al.[9] has suggested a possible association between SABU and poor clinical outcomes in adults with SAB.

We hypothesized that the presence of SABU would identify those patients at increased risk of complications from SAB. SABU may be a practical, economical, and readily available predictor of complicated SAB. Those patients at higher risk for complications may require a more aggressive diagnostic and therapeutic approach.

Methods

We conducted a retrospective cohort study of SAB patients with and without SA in the urine to investigate the association between SABU and the outcomes of the complications and mortality.

The study was conducted at Miami Valley Hospital (MVH, Dayton, OH), an 848-bed, level 1 trauma center with 69 intensive care unit (ICU) beds. MVH is a community teaching hospital affiliated with Wright State University Boonshoft School of Medicine and averages 35,000 admissions per year. The same microbiology laboratory (Compunet Clinical Laboratories) processed all the blood and urine culture specimens of the patients in this study.

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The inclusion criteria were as follows: 1) admission to MVH between January 1, 2004 and December 31, 2007 with a documented episode of SAB (at least 1 positive blood culture); and 2) a documented urine culture within 7 days of the episode of SAB. Patients without a documented urine culture or with inadequate/incomplete treatment for SAB were excluded. A total of 118 patients were included based on the presence of a positive blood culture for SA and the presence of a documented urine culture. Patient electronic and paper records were reviewed by 3 of the investigators (E.V.P.-J., S.D.B., and W.B.B.). Patients subsequently admitted to MVH and to MVH's companion medical center in Dayton, Good Samaritan Hospital, were followed through the electronic medical record common to both institutions.

Study patients were divided into 2 cohorts. One cohort included the patients with a urine culture that grew SA, either methicillin-resistant SA (MRSA) or methicillin-susceptible SA (MSSA). The other cohort included patients who had either a negative urine culture or a positive urine culture with organisms other than SA. The age, sex, date of admission, length of stay, and duration of follow-up were recorded for each patient. Clinical variables included blood culture and urine culture results, presence of intravenous catheters, antibiotic therapy and duration, presence of comorbidities, and clinical outcomes (complications and death).

The primary outcome was complications during hospital admission. The 8 complications investigated were as follows: endocarditis, osteomyelitis, septic arthritis, thrombophlebitis, septic shock, septic embolism/abscess, persistent SAB (lasting more than 5 days after starting adequate SA treatment), and recurrent SAB. In addition, the 2 groups were compared on: 1) any complication, 2) average complications, 3) early complications (ie, within the current hospital admission), and 4) delayed complications (ie, complications diagnosed on subsequent admissions).

Statistical Methods

Means ± standard deviations (SDs) are reported for continuous variables while frequencies and percents are reported for categorical variables. The independent samples *t* test for continuous variables and the chi square test or Fisher's exact test for categorical variables were used to compare the two cohorts. Inferences were made at the 0.05 level of significance with no correction for multiple comparisons. SPSS 11.0 software (SPSS, Inc., Chicago, IL) was used for all analyses.

Results

Of the 118 patients, 58 were female (49.2%) and 60 male (50.8%). The age of the patients was 63.3 ± 16.7 years (mean ± SD). The length of hospital stay was 19.3 ± 17.0 days, and the duration of follow up was 8.3 ± 5.7 months. MRSA was isolated in 75 patients (63.6%) and MSSA in 43 patients (36.4%). In the 28 patients with SA in urine cultures, MRSA was found more frequently than MSSA (20 vs. 8 patients). The acquisition of SAB was equally divided among outpatient (35.6%), healthcare-associated (30.5%), and hospital-acquired (33.9%) settings.

Table 1 shows that the group with SABU did not differ from the group without SABU in age (66 years vs. 62 years; $P = 0.29$), sex (43% male vs. 53% male; $P = 0.33$), length of hospital stay (18 days vs. 20 days; $P = 0.59$), and duration of follow-up (6.6 months vs. 8.8 months; $P = 0.064$). The 2 cohorts also did not differ on the proportion with MRSA bacteremia (71% vs. 61%; $P = 0.32$), origin of SAB ($P = 0.12$), and the presence of comorbidities (diabetes mellitus, cardiomyopathy/congestive heart failure, malignancy, renal disease, and immunosuppression) (all P values > 0.30).

Table 2 shows that patients in the SABU group were nearly twice as likely to have a complication as the group without SABU (64% vs. 33%; $P = 0.004$) and had a higher mean number of complications (0.89 vs. 0.48; $P = 0.016$). Patients in the SABU group also were more likely to have early complications (64% vs. 23%; $P < 0.001$) but no more likely to have a delayed complication (14% vs. 12%; $P = 0.75$). Of the 8 specific complications evaluated, the 2 groups differed only on the presence of septic shock, with the SABU group having 3 times more patients with this complication (21% vs. 7%; $P = 0.035$). Also, a higher proportion of patients died in the SABU group (32.1% vs. 14.4%; $P = 0.036$).

Patients with MRSA (n = 75) and those with MSSA (n = 43) did not differ on any complication, average complications, early or late complications, or 7 of the specific complications (data not shown). Only with thrombophlebitis did the 2 groups differ; the MSSA group had 4 (9.3%) patients with this complication while none in the MRSA group were affected ($P = 0.016$).

Discussion

In our retrospective analysis, SAB with concomitant SABU was associated with more severe disease, complications, and death. Compared to SAB patients without SA in the urine, those with SAB and SA in the urine had more total complications and more early complications, especially septic shock. Further, the proportion of deaths in the SABU cohort was more than twice as high (32% vs. 14%). Therefore, the presence of SABU in patients with SAB could potentially be a useful predictor of complicated SAB and death.

The relationship between SABU and early complications and death remained after excluding the complication of septic shock/need for vasopressors from the analysis (data not shown). The lack of relationship between SABU and delayed complications might have been due to the adequacy of treatment for SAB. Appropriateness of therapy, a criterion for patient inclusion, may have lessened the likelihood of an insufficient treatment plan causing complications. Those patients with MRSA did not differ from those with MSSA on

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TABLE 1. Patient Demographic and Clinical Characteristics

Characteristic	*S. aureus* Bacteriuria (n = 28)	No *S. aureus* Bacteriuria (n = 90)	*P* Value*
Age (years) (mean ± SD)	66.3 ± 16.3	62.4 ± 16.8	0.29
Male sex (n [%])	12 (42.9)	48 (53.3)	0.33
Length of stay (days) (mean ± SD)	17.8 ± 16.1	19.7 ± 17.3	0.59
Follow-up (months) (mean ± SD)	6.6 ± 5.3	8.8 ± 5.7	0.064
Blood culture (n [%])			
MRSA	20 (71.4)	55 (61.1)	0.32
MSSA	8 (28.6)	35 (38.9)	
Origin of the bacteremia [n (%)]			0.12
Community-acquired	13 (46.4)	29 (32.2)	
Healthcare-acquired	10 (35.7)	26 (28.9)	
Hospital-acquired	5 (17.9)	35 (38.9)	
Comorbidities (n [%])			
DM	11 (39.3)	38 (42.2)	0.78
CHF	5 (17.9)	20 (22.2)	0.62
Cancer	7 (25.0)	15 (16.7)	0.32
ESRD	4 (14.3)	12 (13.3)	1.00
Immunosuppression	6 (21.4)	15 (16.7)	0.58
Patients lost to follow-up (n [%])	5 (17.8)	8 (8.8)	0.19

Abbreviations: CHF, congestive heart failure, DM, diabetes mellitus; ESRD, end-stage renal disease; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; SD, standard deviation.

* *t* Test for continuous variables; chi square test or Fisher's exact test for categorical variables.

TABLE 2. Complications and Mortality Comparisons for SABU and No SABU Groups

Outcome	*S. aureus* Bacteriuria (n = 28)	No *S. aureus* Bacteriuria (n = 90)	*P* Value*
Any complication (n [%])	18 (64.3)	30 (33.3)	0.004
Average complications (mean ± SD)	0.89 ± 0.83	0.48 ± 0.77	0.016
Timing of complication (n [%])			
Early	18 (64.3)	21 (23.3)	<0.001
Delayed	4 (14.3)	11 (12.2)	0.75
By specific complication, n (%)			
Endocarditis	1 (3.6)	5 (5.6)	1.00
Osteomyelitis	3 (10.7)	5 (5.6)	0.39
Septic arthritis	2 (7.1)	3 (3.3)	0.59
Thrombophlebitis	1 (3.6)	3 (3.3)	1.00
Septic shock	6 (21.4)	6 (6.7)	0.035
Septic embolism/abscess	6 (21.4)	10 (11.1)	0.21
Persistent SAB	3 (10.7)	3 (3.3)	0.14
Recurrent SAB	3 (10.7)	8 (8.9)	0.72
Death (n [%])	9 (32.1)	13 (14.4)	0.036

Abbreviations: SABU, *Staphylococcus aureus* bacteriuria; SAB, *Staphylococcus aureus* bacteremia; SD, standard deviation.

* *t* Test for continuous variables; chi square test or Fisher's exact test for categorical variables.

the mean number of complications or early and delayed complications. A greater proportion of MSSA patients had thrombophlebitis than MRSA patients.

Other investigations have identified predictors of mortality or complications from SAB,[7,9–12] but SABU was not included as a variable in most of these studies. Fowler et al.[7] proposed a prognostic model of complicated SAB using the predictors from their study; community acquisition of organisms, persistent bacteremia, persistent fever over 72 hours, and skin examination suggestive of an acute systemic infection. Muder et al.[8] reported a relationship between SABU and subsequent SAB, but they did not examine the association between SABU and the risk of complicated SAB. Huggan et al.[9] found that concomitant SABU is associated with ICU admission and increased in-hospital mortality in patients with SAB.

SAB patients with SABU may be at risk for early complications. Consequently, such patients may warrant more aggressive evaluation and treatment. Further, SABU in patients with SAB may be indicative of an "endocarditis-

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like" condition. SA is rarely isolated from the urinary tract as a uropathogen, although it may colonize indwelling catheters and may cause catheter-related urinary tract infections.[13,14] Thus, when present in urine, SA could be a marker of deep tissue dissemination with the potential to cause complications. Guidelines for the management of intravascular device-associated bacteremia have been published by the Infectious Diseases Society of America (IDSA) and other organizations,[15,16] and recent studies have demonstrated the effectiveness of newer agents for the management of SAB.[17] Nevertheless, there is still controversy regarding some aspects of the management of SAB (eg, duration of therapy, criteria for echocardiographic evaluation, role of combination therapy). The presence of SABU, the marker evaluated in our study, may be an additional factor to consider when deciding upon duration of therapy and whether to obtain echocardiography or other imaging.

Our study was limited by its retrospective nature. Patient records were not always complete. For example, not all patients had echocardiography to evaluate for endocarditis or venous ultrasound to evaluate for septic thrombophlebitis. Also, the presence (or proper removal) of intravascular or urinary catheters could not be documented reliably in all patients. In addition, the 7-day cutoff for obtaining urine cultures may have been too lenient, leading to underdiagnosis of bacteriuria. Finally, while 13 patients were lost to follow-up, the 2 groups (SABU and No SABU) did not differ in the proportion lost.

In conclusion, our study found that SABU may be a useful predictor of complicated SAB and death. SAB patients with SABU may be at risk for more and earlier complications. These patients may need closer monitoring due to the higher risk of septic shock and death. Additional therapeutic and management recommendations might include: 1) longer duration of therapy even if a removable source of the bacteremia is identified; 2) more frequent and better supervised follow-up; and 3) imaging studies including either computed tomography (CT) scans or ultrasound for thorough evaluation of complications. Prospective studies including randomized controlled trials are required before implementing these suggested diagnostic and therapeutic recommendations.

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