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PERSPECTIVES

Clinical Significance of *Staphylococcus aureus* in a Single Positive Blood Culture Bottle

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Clinical significance of a single positive blood culture bottle (SPBCB) with *Staphylococcus aureus* is unclear. We aimed to assess the significance of an SPBCB by looking at the associated outcomes. We performed a retrospective, multicenter study of patients with an SPBCB with *S aureus* using data collected from both electronic health records and the clinical microbiology laboratory. Overall, 534 patients with *S aureus* bacteremia were identified and 118 (22.1%) had an SPBCB. Among cases with an SPBCB, 106 (89.8%) were classified as clinically significant whereas 12 (10.2%) were considered contaminated or of unclear significance. A majority (92.4%) of patients received antibiotic therapy, but patients with clinically significant bacteremia were treated with longer courses (25.9 vs 5.7 days, $P < .001$). Significant differences in both frequency of echocardiography (65.1% vs 84.6%, $P < .001$) and infective endocarditis diagnosis (3.8% vs 14.2%, $P = .002$) were seen in those with an SPBCB compared to those with multiple positive bottles. A longer hospital length of stay and higher 90-day, 6-month, and 1-year mortality rates were seen in patients with multiple positive blood culture bottles. An SPBCB with *S aureus* was common among our patients. While this syndrome has a more favorable prognosis as compared to those with multiple positive blood cultures, clinicians should remain concerned as it portends a risk of infective endocarditis and mortality.

Keywords. bacteremia; blood cultures; complications; endocarditis; *Staphylococcus aureus*.

Due to significant morbidity and mortality associated with *Staphylococcus aureus* bacteremia (SAB), finding a single *S aureus*–positive blood culture bottle (SPBCB) from blood culture sets is frequently considered clinically significant. Remarkably, to date, there have been no investigations of the clinical significance of an SPBCB in SAB patients, despite its frequent recognition in clinical microbiology. The local anecdotal experience has been characterized by initiation of antibiotic therapy despite the recognition that *S aureus* can colonize skin and result in blood culture contamination, much akin to that of other commensal bacteria [1]. Of note, coagulase-negative staphylococci are well-recognized as skin flora and a common cause of blood culture contamination and often isolated from only a single blood culture bottle [2].

We therefore investigated cases of SAB with an SPBCB to determine its clinical significance and to understand the rationale of the current practice at multicenter sites of Mayo Clinic.

METHODS

Study Design

We conducted a single healthcare system, multisite, retrospective study of all positive blood cultures for *S aureus*, isolated from adult patients from initial cultures between January 2019 and December 2019 at Mayo Clinic sites in Arizona, Florida, and Minnesota, and the Mayo Clinic Health System in the Midwest. The study was performed following approval from the Mayo Clinic Institutional Review Board. Data were collected from both electronic health records and the clinical microbiology laboratory, and managed using Research Electronic Data Capture [3].

Microbiological Methods

Two blood culture sets were obtained from each patient. The Becton Dickinson BD BACTEC FX platform was used with each blood culture set consisting of 1 BD BACTEC lytic Anaerobic/F bottle and 1 or 2 BD BACTEC Plus Aerobic/F bottles using a standard incubation duration of 5 days. If blood culture bottles flagged positive on the BD BACTEC FX platform, further workup included Gram staining and subculturing onto appropriate media. Identification of *S aureus* was performed by matrix-assisted laser desorption/ionization–time of flight and/or with a combination of morphological and biochemical characteristics. Isolates underwent phenotypic antimicrobial susceptibility testing by agar dilution and results were interpreted using Clinical and Laboratory Standards Institute guidelines.

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Definitions

SAB was defined as having a blood culture with documented growth of *S aureus*. SPBCB was defined as growth of *S aureus* in only 1 of 4–6 blood culture bottles from the index blood culture draw, while multiple positive blood culture bottles (MPBCBs) was defined as growth of *S aureus* in 2 or more blood culture bottles. Charlson Comorbidity Index was used to measure the severity of comorbidities and underlying chronic diseases [4]. Acquisition type was based on Friedman criteria [5]. Community-acquired SAB was defined by a positive blood culture within 48 hours of admission in a patient without prior healthcare involvement whereas healthcare-associated SAB was defined as having a positive blood culture within 48 hours of admission in a patient with prior healthcare involvement. Nosocomial SAB was defined as a positive blood culture identified 48 hours or more after admission. Duration of bacteremia was calculated as days between the first positive and first negative blood culture. Complicated bacteremia was used to describe patients that had 1 or more of the following: infective endocarditis (IE), persistent SAB, septic emboli, presence of intravascular device, hemodialysis, and bacteremia of unclear source, especially in those with community-acquired bacteremia [6]. IE was defined according to the modified Duke criteria [7]. Relapse was defined as isolation of an identical *S aureus* isolate from blood culture within 3 months after antibiotic discontinuation. The clinical significance of SAB was determined by providers at the time of hospitalization and ascertained by the authors based on provider documentation. Cases with documentation of either contamination or of unclear clinical significance by the treating provider were characterized as being clinically insignificant.

Statistical Analysis

Patient characteristics were summarized using means or medians for continuous variables. Categorical variables were reported as counts and percentages. For data comparisons, Kruskal-Wallis rank-sum test, or Fisher exact test for count data, were used as appropriate. A P value of $< .05$ was considered significant. Analyses were performed using R statistical software (version 3.6.2, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Overall, 602 patients with SAB were identified, and 534 met study criteria and were included in the investigation (Supplementary Figure 1). Of them, 118 (22.1%) had an SPBCB, while 416 (77.9%) had MPBCBs. Baseline characteristics and clinical presentations of patients with an SPBCB and MPBCBs were compared and summarized in Table 1.

More patients in the MPBCB group had a cardiac prosthetic device (16.6% vs 7.6%, $P = .017$). MPBCB patients also had a longer duration of SAB (2.8 vs 1.8 days, $P < .001$) and shorter time to blood culture positivity (14.2 hours vs 24.6 hours, $P < .001$) from index blood cultures.

Using the Predicting Risk of Endocarditis Using a Clinical Tool (PREDICT) scoring system [8] to identify patients at higher risk of IE and to determine the need of a transesophageal echocardiogram, no significant difference was seen between those with clinically significant SPBCB as compared to those with MPBCBs; however, significant differences were seen in both frequency of echocardiography use (65.1% vs 84.6%, $P < .001$) and IE diagnosis (3.8% vs 14.2%, $P = .002$) for patients in the SPBCB vs MPBCB group, respectively (Table 2) . Hospital length of stay was longer in the MPBCB group (12.7 vs 9.3 days, $P < .001$). In addition, 90-day, 6-month, and 1-year mortality rates were higher in the MPBCB group compared to patients with clinically significant SPBCB. There was no significant difference in relapse rates between the 2 groups. Among SPBCB cases, 106 (89.8%) were classified as clinically significant while 12 (10.2%) were considered contaminated or of unclear clinical significance. Patient demographics, characteristics, and medical data were similar among the groups and are summarized in Supplementary Table 1. A majority (109 of 118 [92.4%]) of SPBCB cases were treated with antibiotic therapy; patients with clinically significant SAB were treated with longer (25.9 vs 5.7 days, $P < .001$) antibiotic courses. Outcomes between those with an SPBCB (contaminated or of unclear significance vs clinically significant) were similar overall (Table 3).

DISCUSSION

To our knowledge, this is the first study to evaluate the clinical significance of an SPBCB with *S aureus* in patients with at least 2 sets of blood cultures obtained. Importantly, SPBCB was documented in almost one-quarter of SAB cases. Based on local practice, an SPBCB was often regarded as clinically significant and treated with antibiotic therapy. When combined with appropriate follow-up, cases of SAB labeled as contamination after careful assessment by an infectious disease specialist had favorable clinical outcomes [9]. While *S aureus* may cause blood culture contamination, the observation of an SPBCB for *S aureus* should trigger, in our opinion, a thorough investigation and clinical correlation is prudent as its associated mortality remained high, and complications, including IE, were documented. While overall numbers were low, mortality in the contaminant SPBCB group was similar to that of the clinically significant SPBCB group. One study tried to provide interpretation guidelines to differentiate contamination from true bloodstream infection and found a positive predictive value of 100% with 2 or more positive bottles for *S aureus* [10]. Patients with SPBCB were less likely to both require and undergo echocardiography, and prevalence of IE diagnosis was lower as compared to those with MPBCBs. Due to a reduced rate of echocardiography use, it is certainly

Table 1. Clinical Features of Patients With a Single Positive Culture Compared to Those With Multiple Positive Cultures

Characteristic	Single Positive (n = 118)	Multiple Positives (n = 416)	Total (N = 534)	*P* Value
Age, y, mean (SD)	62.7 (17.6)	64.2 (17.3)	63.9 (17.4)	.324[a]
Male sex	65 (55.1)	267 (64.2)	332 (62.2)	.085[b]
Body mass index, kg/m^2, mean (SD)	30.2 (9.5)	29.1 (8.2)	29.3 (8.5)	.415[a]
Charlson Comorbidity Index, mean (SD)	4.9 (3.2)	5.2 (2.9)	5.1 (3.0)	.445[a]
Comorbidities				
Injection drug use	5 (4.2)	25 (6.0)	30 (5.6)	.650[b]
Myocardial infarction	27 (22.9)	126 (30.3)	153 (28.7)	.134[b]
Congestive heart failure	30 (25.4)	139 (33.4)	169 (31.6)	.116[b]
Peripheral vascular disease	14 (11.9)	54 (13.0)	68 (12.7)	.876[b]
Chronic obstructive pulmonary disease	18 (15.3)	47 (11.3)	65 (12.2)	.265[b]
Connective tissue disease	10 (8.5)	46 (11.1)	56 (10.5)	.498[b]
Diabetes mellitus	56 (47.5)	140 (33.7)	196 (36.7)	**.021**[b]
Moderate to severe chronic kidney disease[c]	28 (23.7)	93 (22.4)	121 (22.7)	.803[b]
Malignancy	26 (22.0)	105 (25.2)	131 (24.5)	.545[b]
Cardiac prosthetic device	9 (7.6)	69 (16.6)	78 (14.6)	**.017**[b]
Prosthetic valve	3 (2.5)	24 (5.8)	27 (5.1)	.232[b]
Permanent pacemaker	4 (3.4)	34 (8.2)	38 (7.1)	.102[b]
AICD	1 (0.8)	14 (3.4)	15 (2.8)	.210[b]
CRT	1 (0.8)	3 (0.7)	4 (0.7)	1.000[b]
VAD	1 (0.8)	5 (1.2)	6 (1.1)	1.000[b]
MRSA	31 (26.3)	117 (28.1)	148 (27.7)	.728[b]
Acquisition				.430[b]
Community	44 (37.3)	155 (37.3)	199 (37.3)	
Healthcare-associated	69 (58.5)	228 (54.9)	297 (55.7)	
Nosocomial	5 (4.2)	32 (7.7)	37 (6.9)	
ICU admission	27 (23.1)	122 (29.3)	149 (28.0)	.096[b]
Duration of symptoms >7 d	46 (39.0)	177 (42.5)	223 (41.8)	.527[b]
Daily blood cultures	76 (64.4)	340 (83.1)	416 (78.9)	**<.001**[b]
Duration of BSI, d, mean (SD)	1.8 (1.2)	2.8 (2.2)	2.6 (2.1)	**<.001**[a]
Patients w/ BSI >72 h	15 (14.6)	110 (29.1)	125 (26.0)	**.002**[b]
Time to positivity, h, mean (SD)	24.6 (15.0)	14.2 (5.4)	16.5 (9.5)	**<.001**[a]
PREDICT score day 1, mean (SD)	1.4 (0.8)	1.6 (1.0)	1.6 (1.0)	.076[a]
PREDICT score day 5, mean (SD)	1.7 (1.1)	2.2 (1.4)	2.1 (1.4)	**.003**[a]
Proportion w/ PREDICT >2 on day 5	57 (51.4)	245 (60.8)	302 (58.8)	.082[b]
Complicated bacteremia	59 (50.0)	309 (74.6)	368 (69.2)	.125[b]
Infective endocarditis	4 (3.4)	59 (14.2)	63 (11.8)	**<.001**[b]
Osteomyelitis	14 (11.9)	70 (16.8)	84 (15.7)	.251[b]
No. of patients treated	109 (92.4)	416 (100.0)	525 (98.3)	**.001**[b]
Total antibiotic duration, mean (SD)	23.8 (21.4)	33.0 (26.4)	31.0 (25.7)	**<.001**[a]

Data are presented as No. (%) unless otherwise indicated. Values in bold are statistically significant.

Abbreviations: AICD, automatic implantable cardioverter defibrillator; BSI, bloodstream infection; CRT, cardiac resynchronization therapy; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus*; PREDICT, Predicting Risk of Endocarditis Using a Clinical Tool; SD, standard deviation; VAD, ventricular assist device.

[a]Kruskal-Wallis rank-sum test.

[b]Fisher exact test for count data.

[c]Moderate: creatinine >3 mg/dL (0.27 mmol/L); severe: on dialysis, status post–kidney transplant, uremia.

possible that cases of IE went undiagnosed in patients with SPBCB.

The relatively small sample size and the retrospective nature of this investigation are among its primary limitations. Statistical differences in complications and other outcomes may not have been detected due to the small number of patients. Also, classification of patients in either the significant and of unclear significance groups and the treatment provided were largely defined by providers seeing patients at that time. Factors considered included the patient's clinical presentation, presence of an alternative diagnosis, resolution or bacterial clearance prior to initiation of effective antimicrobial therapy, and the patient's risk profile. A major limitation was the percentage of patients who received antibiotic therapy before repeat blood cultures were obtained, which often enhanced the uncertainty of the true significance of a positive blood culture. Several questions remain and

Table 2. Comparison of Outcomes in Patients With Clinically Significant Single Positive Culture Compared With Those With Multiple Positive Cultures

Characteristic	Clinically Significant, Single Positive (n = 106)	Multiple Positives (n = 416)	Total	*P* Value
Hospital length of stay, d, mean (SD)[a]	9.3 (8.5)	12.7 (14.3)	12.0 (13.5)	**<.001**[b]
Mortality				
30-d mortality (n = 521)	15 (14.2)	79 (19.0)	94 (18.0)	.261[c]
60-d mortality (n = 521)	18 (17.0)	100 (24.1)	118 (22.6)	.152[c]
90-d mortality (n = 521)	18 (17.0)	111 (26.7)	129 (24.7)	**.043**[c]
6-mo mortality (n = 521)	23 (21.7)	132 (31.7)	155 (29.7)	**.043**[c]
1-y mortality (n = 487)	28 (28.3)	158 (40.7)	186 (38.2)	**.027**[c]
90-day relapse	1 (0.9)	18 (4.3)	19 (3.6)	.143[c]
Echocardiography needed based on PREDICT	53 (53.0)	243 (60.3)	296 (58.9)	.212[c]
Echocardiogram performed	69 (65.1)	351 (84.6)	420 (80.6)	**<.001**[c]
Transthoracic	55 (51.9)	268 (64.4)	323 (61.9)	**.019**[c]
Transesophageal	26 (24.5)	205 (49.4)	231 (44.3)	**<.001**[c]
Infective endocarditis	4 (3.8)	59 (14.2)	63 (12.1)	**.002**[c]

Data are presented as No. (%) unless otherwise indicated. Values in bold are statistically significant.

Abbreviations: PREDICT, Predicting Risk of Endocarditis Using a Clinical Tool; SD, standard deviation.

[a]Restricted to patients who survived to hospital discharge.

[b]Kruskal-Wallis rank-sum test.

[c]Fisher exact test for count data.

further studies are needed to determine the best approach in echocardiography use. Also, questions persist as to whether a shorter duration of antibiotic therapy is indicated and whether oral antibiotic treatment may be an option in this cohort.

In summary, patients with an SPBCB may have a more favorable long-term prognosis as compared to that in patients with MPBCBs; SPBCB patients have a lower bacterial burden, as evidenced by a longer time to blood culture positivity, and a shorter duration of bacteremia. Nevertheless, SPBCB is characterized by a lower, but sizable risk of IE and mortality and should therefore not be routinely discounted.

Notes

Patient consent. The study was reviewed by the Mayo Clinic Institutional Review Board (IRB) and was granted an exemption (IRB number 19-005199). Patients who declined authorization to use their medical records for research purposes were excluded from the study.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Table 3. Comparison of Outcomes in Patients With a Single Positive Culture Considered a Contaminant or of Unclear Significance Compared With Those Considered Clinically Significant

Characteristic	Contaminant, Single Positive (n = 12)	Clinically Significant, Single Positive (n = 106)	Total	*P* Value
Hospital length of stay, d, mean (SD)[a]	6.6 (7.0)	9.3 (8.5)	9.0 (8.3)	.270[b]
Mortality				
30-d mortality (n = 118)	0	15 (14.2)	15 (12.7)	.359[c]
60-d mortality (n = 118)	0	18 (17.0)	18 (15.3)	.209[c]
90-d mortality (n = 118)	0	18 (17.0)	18 (15.3)	.209[c]
6-mo mortality (n = 118)	1 (8.3)	23 (21.7)	24 (20.3)	.455[c]
1-y mortality (n = 109)	1 (10.0)	28 (28.3)	29 (26.6)	.284[c]
90-d relapse	0	1 (0.9)	1 (0.8)	1.000[c]

Data are presented as No. (%) unless otherwise indicated.

Abbreviation: SD, standard deviation.

[a]Restricted to patients who survived to hospital discharge.

[b]Kruskal-Wallis rank-sum test.

[c]Fisher exact test for count data.

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