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MAJOR ARTICLE

Limited Clinical Utility of Follow-up Blood Cultures in Patients With Streptococcal Bacteremia: An Opportunity for Blood Culture Stewardship

Emily A. Siegrist,[1,2] Minkey Wungwattana,[1] Leyla Azis,[3] Patricia Stogsdill,[3] Wendy Y. Craig,[4] and Kristina E. Rokas[1]

[1]Pharmacy, Maine Medical Center, Portland, Maine, USA, [2]Pharmacy, University of Oklahoma Medical Center, Oklahoma City, Oklahoma, USA, [3]Infectious Diseases, Maine Medical Center, Portland, Maine, USA, and [4]Maine Medical Center Research Institute, Scarborough, Maine, USA

Background. The value of positive follow-up blood cultures (FUBCs) in streptococcal bacteremia has not been well defined. Therefore, we explored the frequency of and risk factors for positive FUBC in a retrospective cohort of patients with streptococcal bacteremia.

Methods. Adults ≥18 years of age, admitted with at least 1 positive blood culture for *Streptococcus* spp between 2013 and 2018 followed by at least 1 FUBC, were potentially eligible. Positive FUBCs were defined as cultures positive for the same streptococcal species drawn >24 hours after the index culture. We excluded patients with polymicrobial bacteremia. We compared the characteristics of patients with and without a positive FUBC.

Results. In our single-center cohort, we identified 590 patients with streptococcal bacteremia, and 314 patients met inclusion criteria. Ten patients had FUBC with *Streptococcus* spp (3.2%), 4 (1.3%) had a contaminant identified, and 3 (1.0%) had a new pathogen isolated. Endocarditis (5 of 10 [50.0%] vs 35 of 304 [11.5%]), epidural abscess (2 of 10 [20%] vs 4 of 304 [1.3%]), and discitis or vertebral osteomyelitis (3 of 10 [30.0%] vs 14 of 304 [4.6%]) were associated with positive FUBC. Patients with positive FUBC had a longer median length of stay (12.9 vs 7.1 days, $P = .004$) and longer duration of antibiotic treatment (14.9 vs 43.2 days, $P = .03$).

Conclusions. Follow-up blood cultures among patients with streptococcal BSI are rarely positive. Clinicians could consider limiting follow-up blood cultures in patients at low risk for deep-seated streptococcal infections, persistent bacteremia, or endovascular infection.

Keywords. blood cultures; Gram-positive bacteremia; persistent bacteremia; repeat blood cultures; *Streptococcus* spp.

Bloodstream infections (BSIs) are common, with an estimated 10 cases of bacteremia per 1000 hospital admissions [1–3]. Streptococcal bacteremia is of clinical concern because of the predilection of certain streptococcal species to cause endocarditis [4]. Blood culture is currently the standard of care for diagnosing and monitoring BSIs; however, indications for follow-up blood cultures (FUBCs) are not clear [5]. For *Staphylococcus aureus* BSI, data and current guidelines support the utility of FUBC to document clearance and establish a treatment duration [6, 7].

Previous studies that evaluated frequency of persistent bacteremia and factors associated with positive FUBC have included both Gram-positive and Gram-negative bacteremia; however, these studies have limited applicability in streptococcal bacteremia due to their heterogenous cohort and small numbers of streptococcal isolates included [8–10]. The purpose of our study was to determine the frequency of positive FUBC in patients with streptococcal bacteremia and to identify risk factors for positive FUBC.

METHODS

This study was performed at Maine Medical Center, a tertiary care center in Portland, Maine and was approved by the Maine Health Institutional Review Board. Patients were eligible for this study if they were ≥18 years of age, admitted between January 1, 2013 and December 31, 2018, had a blood culture positive for any streptococcal species, and received an FUBC. Patients were excluded if the index blood culture was polymicrobial, if the patient died within 48 hours of index culture, if index cultures were drawn at an outpatient facility, or if no FUBCs were collected. If a patient had >1 incidence of streptococcal bacteremia within the study period, only the first admission was included. The BD BACTEC blood culture system was used for detection of positive blood cultures. BD Phoenix automated identification and susceptibility testing system was used through the study period. In October 2015, Verigene Nanosphere was implemented for rapid streptococcal isolate identification.

Chart review was used to collect data from electronic medical records. Data collected included basic demographics, microbiology

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Correspondence: Kristina E. Rokas, Maine Meidcal Center, 22 Bramhall St., Portland, ME 04102 (KristinaConnolly2@mmc.org).

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data, time to antibiotic start, duration of antibiotic treatment, intensive care unit admission, length of stay, in-hospital and 30-day mortality, infectious diseases (ID) consult, echocardiogram results, comorbidities, presumed source of bacteremia, source control procedures, patient disposition, and antibiotic therapy at discharge. Data collection included initial timing and selection of antibiotic, history of valve replacement, diagnosis of endocarditis, discitis or vertebral osteomyelitis or epidural abscess, transthoracic echocardiogram (TTE) or transesophageal echocardiogram abnormalities during inpatient stay, time to ID consult, fever 2 hours prior to repeat culture, length of stay, and duration of antibiotic treatment. The primary outcome of this study was to determine the frequency of positive FUBC in streptococcal bacteremia. The secondary outcome was to determine risk factors associated with positive streptococcal FUBC. Particular characteristics of interest included sources of infection that were deep-seated including endocarditis, vertebral osteomyelitis, and epidural abscess, fever prior to FUBC, initial selection and timing of antibiotics, and duration of hospitalization and antimicrobial therapy.

Patient Consent Statement

Informed consent was waived due to the retrospective design. The design of this work was approved by Maine Medical Center Institutional Review Board and conforms to standards currently applied in the United States.

Definitions

Our definitions include the following terms: (1) community-acquired bacteremia - positive blood cultures <48 hours after hospital admission; (2) contaminant - cultures positive for *Corynebacterium*, coagulase negative *Staphylococci*, or *Bacillus* species in only 1 blood culture set; (3) duration of bacteremia - difference between collection time of index blood culture and collection time of first negative blood culture; (4) follow-up blood culture - blood culture drawn >24 hours after index culture is collected during same hospitalization as index culture; (5) index culture - the first culture or set of cultures drawn (cultures drawn ≤24 hours apart were considered part of the index set of cultures); (6) polymicrobial bacteremia - bacteremia with >1 organism identified; (7) repeat positive bacteremia - a blood culture drawn >24 hours after the index culture which is positive for the same streptococcal species while on antibiotics to which the organism is susceptible; (8) source control - incision and drainage, surgical procedure, interventional radiology drain placement, or removal of catheter, intravascular device, or hardware; (9) prior valve replacement - valve replacement before admission; and (10) TTE abnormality - any abnormality on TTE read by cardiologist as possible infective endocarditis.

Statistical Analysis

Data were summarized using descriptive statistics: continuous data were expressed as mean (standard deviation) or median (interquartile range [IQR]), as appropriate, and categorical data are shown as frequency (n, %). Data were shown overall and after stratification by positive follow-up cultures and negative follow-up cultures. Differences in treatment characteristics and outcome measures between subgroups were analyzed using the χ^2 test or Fisher's exact test (categorical variables) or by 2-sided Student's *t* test or Mann-Whitney *U* test (continuous variables), as appropriate. Differences were interpreted after Bonferroni's correction for multiple comparisons. All analyses were performed using SPSS Statistical Software version 25 (IBM SPSS Inc., Armonk, NY).

RESULTS

Of 590 patients with *Streptococcus*-positive initial blood cultures, 314 met inclusion criteria (Figure 1). In the index blood culture, 68.5% of patients had 2 or more initial sets positive for the same species. Of the 314 patients who had at least 1 FUBC, 78 (24.8%) had 2, 31 (9.9%) had 3, 11 (3.5%) had 4, 5 (1.6%) had 5, and 2 (0.6%) had 6 repeat cultures. Among included patients, alpha streptococcal species were isolated most commonly. Alpha streptococcal species were identified in 104 patients (33.1%), whereas *Streptococcus pneumoniae* was isolated in 52 (16.6%). Of patients with the beta-hemolytic streptococci isolated, Group B streptococcus was isolated in 67 (21.3%), Group A streptococcus in 36 (11.5%), Group G streptococcus in 24 (7.6%) and Group C streptococcus in 17 (5.4%). Among patients who had more than 1 FUBC, once blood culture negativity was achieved, all subsequent repeat cultures remained negative. The number of FUBCs drawn were similar among different *Streptococcus* spp (data not shown). Of the 314 included patients, only 10 (3.2%) had positive FUBC. Four patients (1.3%) had a contaminant found in FUBC. Three patients (1.0%) had an index culture positive for *Streptococcus* alone, but different pathogens were identified in subsequent

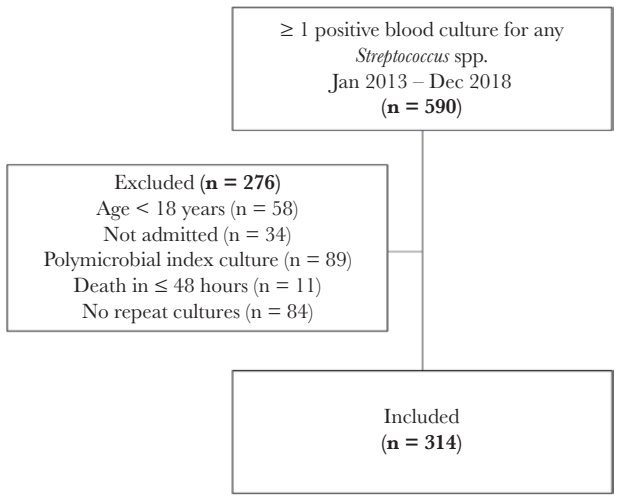

Figure 1. Flow chart for inclusion and exclusion in the study

FUBC. Of the 10 patients with positive streptococcal FUBC, 4 were identified with alpha-hemolytic streptococci not further identified, 3 with group B beta-hemolytic streptococci, 2 with *Streptococcus anginosus* group, and 1 with group G beta-hemolytic streptococci.

Table 1 shows baseline and clinical characteristics of the cohort, both overall and stratified by FUBC result. Patients included were predominantly male. The most frequent comorbidities were hypertension and diabetes, both before and after stratification by FUBC result; intravenous drug use was also frequent among those with a positive FUBC. Presence of indwelling lines or devices and immunocompromised status were uncommon (<5%) at baseline.

Table 2 summarizes presumed infection sources, which were identified for 72.3% of patients; data are shown overall and after stratification by FUBC result. The most common presumed sources were cellulitis (20.4%), respiratory tract infection (15.3%), and infective endocarditis (12.7%). The frequencies of endocarditis (5 of 10 [50.0%] vs 35 of 304 [11.6%]), epidural abscess (2 of 10 [20%] vs 4 of 304 [1.3%]), and discitis or vertebral osteomyelitis (3 of 10 [30.0%] vs 14 of 304 [4.6%]) as presumed sources of infection all demonstrated a trend to higher frequency among patients with positive FUBC.

Table 3 summarizes the treatment characteristics and outcomes of the cohort, overall and after stratification by FUBC result. Median duration of bacteremia was 41.7 hours (IQR, 32.1–54.2). Source control procedures occurred in 23.9% of the cohort and was most commonly abscess drainage (30 patients). Cardiac valve replacement occurred in 15 of 40 patients with endocarditis. All-cause in-hospital mortality was low at 3.2% overall, as was 30-day mortality (5.4% overall). An antibiotic with streptococcal activity was started in 292 (93%) patients in our cohort. The most common antibiotics selected were vancomycin (74.2%), followed by piperacillin-tazobactam (29.3%), cefepime (27.4%), and ceftriaxone (24%). All 10 patients with positive FUBC had appropriate antibiotics started within 24 hours of index culture, compared with only 92.8% (282 of 304) of patients with negative FUBCs.

Table 3 also summarizes primary outcome measures among patients with and without positive FUBC. Among patients with positive FUBC, frequency of prior valve replacement (30% vs 8.9%, $P = .06$), length of stay (12.9 vs 7.1 days $P = .004$), and duration of antibiotics (43.2 vs 14.9 days, $P = .03$) were higher than in those with negative FUBC.

DISCUSSION

Our study found that the presence of endocarditis was associated with positive FUBCs. This is consistent with large observational cohorts which reported that endovascular sources of infection were more likely to have positive FUBC [9, 10].

Table 1. Baseline Demographic and Clinical Characteristics of Cohort, Overall and Stratified by Follow-up Blood Culture Result[a]

	Follow-up Blood Culture Result for *Streptococcus* spp		
Characteristic	Overall (n = 314)	Negative FUBC (n = 304)	Positive FUBC (n = 10)
Male gender	203 (64.6)	196 (64.5)	7 (70)
Age, year, mean (STD) [range]	62.0 (16.7) [20.2–94.6]	62.2 (16.7)	56.0 (16.3)
BMI, kg/m^2, median (IQR)	27.7 (24.1–34.2)	27.7 (24.0–34.5)	26.8 (24.4–33.0)
Surgical admission	23 (7.3)	23 (7.6)	0 (0)
Comorbidities			
Hypertension	163 (51.9)	161 (53.0)	2 (20.0)
Diabetes mellitus	94 (29.9)	91 (29.9)	3 (30.0)
Malignancy	35 (11.1)	35 (11.5)	0 (0)
Neutropenia	11 (3.5)	11 (3.6)	0 (0)
HIV	3 (1.0)	3 (1.0)	0 (0)
AIDS	1 (0.3)	1 (0.3)	0 (0)
Dialysis	10 (3.2)	10 (3.3)	0 (0)
IV drug use	21 (6.7)	19 (6.3)	2 (20.0)
Pregnancy	2/111 (1.8)	2/108 (1.9)	0 (0)
Transplant	8 (2.5)	8 (2.6)	0 (0)
Valve replacement	30 (9.6)	27 (8.9)	3 (30.0)
Intravascular Devices/Lines			
Vascular graft	6 (1.9)	6 (2.0)	0 (0)
Pacemaker/ICD	15 (4.8)	15 (4.9)	0 (0)
LVAD	1 (0.3)	1 (0.3)	0 (0)
Mediport	9 (2.9)	9 (3.0)	0 (0)
Fever 2 hours prior to repeat culture	28/309 (9.1)	27/299 (9.0)	1/10 (10.0)

Abbreviations: AIDS, acquired immunodeficiency syndrome; BMI, body mass index; FUBC, follow-up blood culture; HIV, human immunodeficiency virus; ICD, implantable cardioverter-defibrillator; IV, intravenous; IQR, interquartile range; LVAD, left ventricular assist device; STD, standard deviation.

[a]All data are n (%) unless otherwise indicated.

Table 2. Presumed Source of Bacteremia, Overall and After Stratification by Follow-Up Blood Culture Result[a]

	Follow-up Blood Culture Result for *Streptococcus* spp		
Source of Infection	Overall (n = 314)	Negative (n = 304)	Positive (n = 10)
None identified	86 (27.4)	85 (28.0)	1 (10.0)
Skin and skin structure	64 (20.4)	64 (21.1)	0 (0)
Respiratory	48 (15.3)	48 (15.8)	0 (0)
Endocarditis	40 (12.7)	35 (11.5)	5 (50.0)
Discitis/vertebral osteomyelitis	17 (5.4)	14 (4.6)	3 (30.0)
Gastrointestinal	11 (3.5)	11 (3.6)	0 (0)
Meningitis	10 (3.2)	10 (3.3)	0 (0)
Nonvertebral osteomyelitis	9 (2.9)	9 (3.0)	0 (0)
Septic arthritis	8 (2.5)	8 (2.6)	0 (0)
Dental	7 (2.2)	6 (2.0)	1 (10.0)
Epidural abscess	6 (1.9)	4 (1.3)	2 (20.0)
Diabetic foot infection	6 (1.9)	6 (2.0)	0 (0)
UTI	6 (1.9)	6 (2.0)	0 (0)
Prosthetic joint	4 (1.3)	4 (1.3)	0 (0)
Catheter-associated	2 (0.6)	2 (0.7)	0 (0)
Intravascular device	2 (0.6)	2 (0.7)	0 (0)
Other	38 (12.1)	35 (11.5)	3 (30.0)

Abbreviations: UTI, urinary tract infection.

[a]Patients could have multiple sources identified. All data are n (%).

Excess repeat blood cultures can lead to increased isolation of contaminants and increased costs to laboratory and pharmacy [11]. Contaminants can often be difficult for providers to differentiate from true infections and can result in unnecessary hospitalizations and antibiotic administration [12]. Clinicians may consider obtaining FUBC in patients with high suspicion for invasive infection where it may change management. Nonetheless, negative FUBC cannot exclude the presence of a serious infection in patients bacteremic with streptococci.

Previous studies have shown that there are low rates of bacteremia in patients with cellulitis and nonsevere community-acquired pneumonia (CAP) [5, 13]. For nonsevere CAP, blood cultures are not recommended due to low probability that the results will change the treatment regimen [14, 15]. However, blood cultures are still recommended for patients presenting with sepsis or severe CAP. We did not assess appropriateness of the initial blood culture; however, we presume they were appropriate given the positive blood culture results. In addition, we did not observe any patients in our cohort with either respiratory or skin and soft tissue as a source of infection who had positive FUBC, which further emphasizes the lack of clinical utility of repeat blood cultures in these patient populations.

Our study did not find a significant association between fever within 2 hours of FUBC and a positive FUBC result for patients with streptococcal bacteremia. Fever has been an inconsistent predictor of positive FUBC in previous literature. Canzoneri et al [8] found that fever within 2 hours of FUBC collection was associated with both Gram-positive and Gram-negative bacteremia. However, this study had higher rates of patients on hemodialysis or with indwelling lines and also had a small population of patients with streptococcal bacteremia, which may have contributed to this difference. Some previous studies have evaluated the utility of fever for prediction of initial blood culture results and have found that fever alone was a poor predictor of bacteremia [16]. Although

Table 3. Treatment Characteristics and Outcomes of Patients, Overall and After Stratification by Follow-Up Blood Culture Result

	Follow-up Blood Culture Result for *Streptococcus* spp			
	Overall (n = 314)	Negative (n = 304)	Positive (n = 10)	*P* Value
Outcomes				
Duration of bacteremia, hours, median (IQR)	**41.7 (32.1–54.2)**	**41.5 (32.0–53.0)**	**69.0 (48.7–84.7)**	**.007**[a]
ICU admission	98 (31.2)	93 (30.6)	5 (50.0)	.30[b]
In-hospital mortality	10 (3.2)	10 (3.3)	0 (0)	1.00[b]
30-day mortality	17/286 (5.9)	17/278 (6.1)	0/8 (0)	.28[b]
Length of stay, days, median (IQR)	**7.2 (5.0–12.9)**	**7.1 (4.9–12.8)**	**12.9 (10.9–26.7)**	**.004**[b]
Discharge to home	189 (60.4)	182 (60.1)	7 (70.0)	.74[b]
Treatment characteristics				
Initial treatment with beta-lactam	251 (79.9)	245 (80.6)	6 (60.0)	.12[a]
Antibiotic with streptococcal activity initiated within 24 hours of index culture	292 (93.0)	282 (92.8)	10 (100.0)	1.00[b]
Time to antibiotic treatment, hour	0.87 (0.28–3.31)	0.87 (0.28–3.03)	2.32 (0.58–10.8)	.23[a]
Total duration of antibiotic therapy, day (IQR) (n = 223–217, 6)	15.5 (13.9–30.1)	15.4 (13.7–29.8)	35.5 (20.9–44.5)	.03[a]
Nonmedical Interventions				
ID consult	**169 (53.8)**	**159 (52.3)**	**10 (100.0)**	**.002**[b]
Time to ID consult	42.5 (21.1–75.6)	41.6 (21.1–74.6)	49.5 (34.9–117.0)	.34[a]

Abbreviations: ICU, intensive care unit; ID, infectious diseases; IQR, interquartile range.

NOTE: All data are n (%) or as median (IQR).

[a]Mann-Whitney *U* test.

[b]Fisher's exact test. Statistically significant findings are shown in bold. Significance was accepted at $P < .008$ for both treatment characteristics and outcome measures after Bonferroni correction for multiple comparisons.

temperature alone may not be the most reliable predictor of bacteremia, several studies have demonstrated that fever in conjunction with other factors may be useful when evaluating a patient's pretest probability [13, 17]. Our results suggest that fever alone may not be a useful predictor of positive FUBC in streptococcal bacteremia.

This study had several limitations. This was a retrospective cohort study limited by the information available in the medical record. We also cannot exclude the possibility that some of the streptococcal species isolated in only 1 blood culture set could be considered contaminants. We chose to include any patient with at least 1 positive culture for streptococci because this cohort reflects the yield of FUBC in a real-world setting; therefore, it is possible that some streptococcal contaminants were included in the analysis. Furthermore, the inclusion of single sets of blood cultures in this study may contribute to overestimation of negative FUBC. In our cohort, we had 31.5% of isolates that had only 1 of 2 blood culture sets positive. 84 patients included in this study did not receive a FUBC, and there is lack of documentation on rationale for FUBCs in medical records, which limits some interpretation of FUBC results. Immunocompromised patients were underrepresented in our cohort, and our findings cannot be extrapolated to this patient population. Finally, these analyses are limited by a small number of repeat positive blood cultures.

CONCLUSIONS

In conclusion, our study demonstrates that FUBCs have limited utility in streptococcal bacteremia. Antimicrobial stewardship programs may benefit from incorporating blood culture stewardship to limit repeat cultures in patients at low risk for serious streptococcal infections. Clinicians could consider limiting FUBCs in patients at low risk for deep-seated streptococcal infections, persistent bacteremia, or endovascular infection.

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