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

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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 vs 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.
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, transesophageal 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 χ² 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
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 Resulta

| 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/m², 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.

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

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

| 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.
*Patients could have multiple sources identified. All data are n (%).

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

| Outcomes                                      | Overall (n = 314) | Negative (n = 304) | Positive (n = 10) | P-Value  |
|-----------------------------------------------|-------------------|--------------------|-------------------|----------|
| Duration of bacteremia, hours, median (IQR)   | 41.7 (32.1–54.2)  | 41.5 (32.0–53.0)   | 69.0 (48.7–84.7)  | .007b    |
| ICU admission                                 | 98 (31.2)         | 93 (30.6)          | 5 (50.0)          | .30b     |
| In-hospital mortality                         | 10 (3.2)          | 10 (3.3)           | 0 (0)             | 1.00b    |
| 30-day mortality                              | 17/286 (5.9)      | 17/278 (6.1)       | 0/8 (0)           | .28b     |
| Length of stay, days, median (IQR)            | 7.2 (5.0–12.9)    | 7.1 (4.9–12.8)     | 12.9 (10.9–26.7)  | .004b    |
| Discharge to home                             | 189 (60.4)        | 182 (60.1)         | 7 (70.0)          | .34b     |
| Initial treatment with beta-lactam            | 251 (79.9)        | 245 (80.6)         | 6 (60.0)          | .12b     |
| Antibiotic with streptococcal activity initiated within 24 hours of index culture | 292 (93.0) | 282 (92.8) | 10 (100.0) | 1.00b |
| Time to antibiotic treatment, hour            | 0.87 (0.28–3.31)  | 0.87 (0.28–3.03)   | 2.32 (0.58–10.8)  | .23b     |
| Total duration of antibiotic therapy, day (IQR) | 15.5 (13.9–30.1)  | 15.4 (13.7–29.8)   | 35.5 (20.9–44.5)  | .03b     |

Abbreviations: ICU, intensive care unit; ID, infectious diseases; IQR, interquartile range.
*NOTE: All data are n (%) or as median (IQR).
*Mann-Whitney U test.
*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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**References**

1. Leibovici L, Samra Z, Konigsberger H, et al. Long-term survival following bacteremia or fungemia. JAMA 1995; 274:807–12.
2. Rodríguez-Baño J, Lopez-Prieto MD, Portillo MM, et al. Epidemiology and clinical features of community-acquired, healthcare-associated and nosocomial bloodstream infections in tertiary care and community hospitals. Clin Microbiol Infect 2010; 16:1408–13.
3. Sogaard M, Norgaard M, Dethlefsen C, Schonheyder HC. Temporal changes in the incidence and 30-day mortality associated with bacteremia in hospitalized patients from 1992 through 2006: a population-based cohort study. Clin Infect Dis 2011; 52:61–9.
4. Chamat S, Dahl A, Østergaard L, et al. Prevalence of infective endocarditis in streptococcal bloodstream infections is dependent on streptococcal species. Circulation 2020; 142:720–30.
5. Fabre V, Sharara SL, Salinas AB, et al. Does this patient need blood cultures? A scoping review of indications for blood cultures in adult nonneutropenic patients. Clin Infect Dis 2020; 71:1339–47.
6. Liu C, Bayer A, Cosgrove SE, et al.; Infectious Diseases Society of America. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clin Infect Dis 2011; 52:e18–55.
7. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis 2009; 49:1–45.
8. Canzoneri CN, Akhavan BJ, Tourz O, et al. Follow-up blood cultures in Gram-negative bacteremia: are they needed? Clin Infect Dis 2017; 65:1776–9.
9. López Dupla M, Martinez JA, Vidal F, et al. Clinical characterization of breakthrough bacteremia: a survey of 392 episodes. J Intern Med 2005; 254:172–80.
10. Wiggers JB, Xiong W, Daneman N. Sending repeat cultures: is there a role in the management of bacteremic episodes? (SCRIERE study). BMC Infect Dis 2016; 16:286.
11. Bates DW, Goldman L, Lee TH. Contaminant blood cultures and resource utilization: the true consequences of false-positive results. J Am Med Assoc 1991; 265:365–9.
12. Thuler LC, Jeniecik M, Turgeon JP, et al. Impact of a false positive blood culture result on the management of febrile children. Pediatr Infect Dis J 1997; 16:846–51.
13. Coburn B, Morris AM, Tomlinson G, Detsky AS. Does this adult patient with suspected bacteremia require blood cultures? JAMA 2012; 308:502–11.
14. Afshar N, Tabas J, Afshar K, Silbergliet R. Blood cultures for community-acquired pneumonia: are they worthy of two quality measures? A systematic review. J Hosp Med 2009; 4:112–23.
15. Mellay JP, Waterer GW, Long AG, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med 2019; 200:e45–67.
16. Linsenmeyer K, Gupta K, Smyth JS, et al. Culture if spikes? Indications and yield of blood cultures in hospitalized medical patients. J Hosp Med 2016; 11:336–40.
17. Shapiro NI, Wolfe RE, Wright SR, et al. Who needs a blood culture? A prospectively derived and validated prediction rule. J Emerg Med 2008; 35:255–64.

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