*Clinical Infectious Diseases*

MAJOR ARTICLE

# Follow-up Blood Cultures in Gram-Negative Bacteremia: Are They Needed?

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***Background.*** Bloodstream infections remain a major cause of morbidity and mortality. Gram-negative bacilli (GNB) bacteremia is typically transient and usually resolves rapidly after the initiation of appropriate antibiotic therapy and source control. The optimal duration of treatment and utility of follow-up blood cultures (FUBC) have not been studied in detail. Currently, the management of gram-negative bacteremia is determined by clinical judgment. To investigate the value of repeat blood cultures, we analyzed 500 episodes of bacteremia to determine frequency of FUBC and identify risk factors for persistent bacteremia.

***Methods.*** Of 500 episodes of bacteremia, we retrospectively analyzed 383 (77%) that had at least 1 FUBC. We sought information regarding presumed source of bacteremia, antibiotic status at the time of FUBC, antibiotic susceptibility, presence of fever, comorbidities (intravenous central lines, urinary catheters, diabetes mellitus, AIDS, end-stage renal disease, and cirrhosis), need for intensive care, and mortality.

***Results.*** Antibiotic use did not affect the rate of positivity of FUBC, unless bacteria were not sensitive to empiric antibiotic. Fever on the day of FUBC was associated with higher rates of positive FUBC for gram-positive cocci (GPC) but not GNB. Mortality and care in the intensive care unit were not associated with positive FUBC. Seventeen FUBC and 5 FUBC were drawn for GNB and GPC to yield 1 positive result.

***Conclusions.*** FUBC added little value in the management of GNB bacteremia. Unrestrained use of blood cultures has serious implications for patients including increased healthcare costs, longer hospital stays, unnecessary consultations, and inappropriate use of antibiotics.

**Keywords.** gram-negative bacteremia; blood cultures; persistent bacteremia; cost containment; false-positive blood culture.

Bloodstream infections remain a major cause of morbidity and mortality despite the availability of potent antimicrobial therapy and advances in supportive care. It is estimated that gram-negative bacilli (GNB) are the cause of approximately a quarter to half of all bloodstream infections. Gram-negative sepsis carries a mortality rate of 12%–38% [1]. Timely and appropriate antimicrobial therapy has been shown to reduce mortality among patients with gram-negative bacteremia; however, the optimal duration of treatment has not been studied in detail. Currently, the duration of therapy is determined by clinical judgment, which accounts for the source of primary infection and the patient's clinical response. This is in stark contrast to gram-positive bacteremia, like that caused by *Staphylococcus aureus*, for which numerous studies have investigated the optimal duration of antibiotic therapy. It is considered standard of care that patients with uncomplicated *S. aureus* bacteremia should be treated with 14 days of intravenous therapy from the first negative blood culture. This necessitates that follow-up blood cultures (FUBCs) be drawn at 2- to 4-day intervals until negative conversion [2]. Gram-negative bacteremia, however, is usually transient, and has not been shown to require follow-up blood cultures [3]. Despite its questionable utility, there is evidence of ongoing unrestrained blood culture use in the setting of gram-negative bacteremia [4]. Given the cost and overall low yield of blood cultures, the use of repeat blood cultures should continue to be scrutinized [5].

To investigate the value of repeat blood cultures, we analyzed 500 episodes of bacteremia to determine frequency of FUBCs and identify risk factors for persistent bacteremia.

## METHODS

### Study Population

The study was undertaken at Lyndon B. Johnson Hospital, a tertiary care center in Houston, Texas, after obtaining institutional review board approval (protocol HSC-MS-16–0794); patient consent requirements were waived. Patients eligible for the study were ≥18 years of age, admitted between 1 January and 31 December 2015 with true bacteremia. We excluded cultures positive for fungal species.

Received 22 May 2017; editorial decision 7 July 2017; accepted 24 July 2017.

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**Clinical Infectious Diseases® 2017;XX(00):1–4**



DOI: 10.1093/cid/cix648

### Data Collection and Analysis

From the medical records that met inclusion criteria, we extracted the following: demographic data, presumed source of bacteremia, antibiotic status at the time of follow-up cultures, antibiotic susceptibility, if the patients were febrile, comorbidities (intravenous central lines, urinary catheters, diabetes mellitus, AIDS, end-stage renal disease [ESRD], and cirrhosis), need for intensive care, and mortality associated with the admission. We determined the number of follow-up cultures drawn for each episode. The duration of bacteremia (in days) among patients with FUBCs was calculated by subtracting the initial date of positive culture from the latest date of positive culture growing the same bacteria, as long as the last set of positive cultures was drawn at least 24 hours after the initial culture. Finally, we calculated the yield of FUBCs by dividing the number of positive results for the total number of FUBCs requested per category of microorganism.

### Definitions

- True bacteremia: at least 1 positive blood culture, not otherwise considered a contaminant.
- Contaminant: a positive blood culture in which the isolate was a common skin organism (such as diphtheroids, micrococci, or coagulase-negative staphylococci) isolated in 1 bottle, or when the medical records reported the positive cultures as contaminants.
- Persistent bacteremia: positive blood cultures for the same original organism in a sample drawn at least 24 hours after the initial culture. We considered any positive blood culture within 24 hours of the first positive as being part of the same episode.
- Medical disease (vs surgical disease): disease in which the source of bacteremia does not require surgical resolution. Of note, in our series, intravenous catheter–related infections were categorized as medical diseases, even when the resolution required the surgical removal of the source.
- Serious skin infections: severe cellulitis, necrotizing fasciitis, and skin abscesses.
- Febrile: Patients were considered febrile if their recorded temperature was >100.4°F (38°C) when at least 1 of the FUBCs was drawn.

### Statistical Analysis

MedCalc version 12.3.0 software (MedCalc Software, Mariakerke, Belgium) was used in the statistical analysis. Categorical variables were analyzed using the Fisher exact test. A 2-sided $P < .05$ was considered statistically significant.

## RESULTS

Five hundred episodes of bacteremia were analyzed. Of those, 383 (77%) had at least 1 FUBC after the initial blood culture. This varied depending on the category of microorganism as follows: gram-positive cocci (GPC), 54%; GNB, 37%; polymicrobial, 8%. On average, our cohort had 2.37 FUBCs per patient (range, 1–12 blood cultures), 2.32 (range, 1–12) per patient in the case of GPC, and 2.32 (range, 1–6) per patient in GNB. The follow-up lasted an average of 4.45 days (range, 1–18 days).

Of the 383 patients with FUBCs, 55 (14%) had positive results, 43 (78%) of which were positive for GPC, and 8 (15%) for GNB. Mean duration of bacteremia was 2.83 days, with a range of 1–15 days. Persistent bacteremia was more common for GPC (21%) than polymicrobial infection (10%) than GNB (6%). The mean duration of bacteremia was comparable for the 3 categories of microorganisms (2.8, 2.9, and 2.7, days, respectively). Characteristics of the patients with FUBC are presented in Table 1. The FUBC were positive for *Staphylococcus aureus* (31), coagulase-negative staphylococci (6), *Enterococcus* (4), group B *Streptococcus* (1), and *Streptococcus pneumoniae* (1) for GPC; and *Escherichia coli* (5), *Klebsiella pneumonia*, *Serratia marcescens*, and *Stenotrophomonas maltophilia* (1 each) for GNB.

The differences between patients whose FUBCs were positive or negative are presented in Table 2. The same comparison, but specific for GPC and GNB, is presented in Table 3. The number of positive FUBCs in the GNB group was too small, resulting in a cautious analysis. The use of antibiotics did not make a difference in the rate of positivity of FUBCs. The presence of fever on the

**Table 1. Characteristics of Patients With Follow-up Blood Cultures (n = 383)**

| Characteristic | No. (%) |
|---|---|
| Male sex | 211 (55) |
| Age, y, mean ± standard deviation | 53 ± 15 |
| Known source of bacteremia | 273 (71) |
| Medical (vs surgical) disease | 314 (82) |
| Initial bacteremia caused by | |
| Gram-positive cocci | 206 (53.8) |
| Gram-negative bacilli | 140 (37) |
| Polymicrobial | 30 (8) |
| Gram-positive bacilli | 6 (1.6) |
| Anaerobes | 1 (0.3) |
| Patients on antibiotics the day of FUBC | 347 (91) |
| Microorganism sensitive to those antibiotics | 325 (85) |
| Fever on the day of FUBC | 127 (33) |
| Presence of an IV central line | 165 (43) |
| Presence of a bladder catheter or nephrostomy | 119 (31) |
| Neutropenia (ANC < 1000/mL) | 36 (9) |
| Diabetes mellitus | 230 (60) |
| AIDS | 28 (7) |
| ESRD on hemodialysis | 92 (24) |
| Liver failure | 53 (14) |
| Need for ICU care | 165 (43) |
| In-hospital death | 52 (14) |

Abbreviations: ANC, absolute neutrophil count; ESRD, end-stage renal disease; FUBC, follow-up blood culture; ICU, intensive care unit; IV, intravenous.

**Table 2. Differences Between Patients Whose Follow-up Blood Cultures Were Positive or Negative**

| Characteristic | Positive (n = 55) | | Negative (n = 328) | | *P* Value |
|---|---|---|---|---|---|
| On antibiotics when cultures drawn | 54 | 98% | 312 | 95% | .49 |
| Medical disease (vs surgical) | 49 | 89% | 265 | 81% | .18 |
| Fever when cultures drawn | 27 | 49% | 100 | 30% | **.008** |
| Presence of a urinary catheter | 11 | 20% | 82 | 25% | .50 |
| Presence of an IV central catheter | 34 | 62% | 121 | 37% | **<.001** |
| Neutropenia (ANC <1000/mL) | 4 | 7% | 29 | 9% | 1.00 |
| Diabetes mellitus | 31 | 56% | 121 | 37% | .19 |
| HIV positive | 3 | 5% | 20 | 6% | 1.00 |
| ESRD on hemodialysis | 24 | 44% | 65 | 20% | **<.001** |
| Liver cirrhosis | 5 | 9% | 33 | 10% | 1.00 |
| ICU care required | 18 | 33% | 119 | 36% | .65 |
| Death | 3 | 5% | 35 | 11% | .33 |

Data are presented as No. (%) unless otherwise indicated. Bold numbers represent those statistically significant.

Abbreviations: ANC, absolute neutrophil count; ESRD, end-stage renal disease; HIV, human immunodeficiency virus; ICU, intensive care unit; IV, intravenous.

day of FUBC was associated with higher rates of positive FUBCs. Twenty-one of 24 (87%) patients with ESRD who had positive FUBCs obtained their dialysis through a central intravenous line. However, the FUBC were drawn from a peripheral vein. Twenty-nine of the 71 (41%) patients with positive FUBC and diagnosis of urinary tract infection had some form of urinary catheter. Diabetes mellitus, ESRD, and the presence of a central intravenous line made the rate of positive FUBCs for GPC higher.

The source of bacteremia was known in 273 (71%) of the patients who had FUBCs. Thirty-seven of those patients had positive FUBCs, and 236 had negative FUBCs. The relative incidence of bacteremia for each source can be found on Table 4. While urinary tract and severe skin infections seemed negatively associated with positive FUBCs, intravenous catheter infections increased the probability of positive FUBCs. Mortality and care in the intensive care unit were not associated with positive FUBCs.

In our cohort, approximately 5 FUBCs were needed to yield 1 positive result; however, when considering only GNB bacteremia, it took 17 FUBCs to yield 1 positive result.

## DISCUSSION

In our study, persistent bacteremia occurred more commonly in GPC infections than in GNB infections. Patients who were febrile on the day of FUBC had higher rates of positive FUBCs. Patients with diabetes mellitus, intravenous central lines, or ESRD had significantly increased rates of positive FUBC for GPC but not GNB. Positive FUBCs for all bacteremic infections demonstrated no association with higher intensive care unit admissions or mortality, further supporting the limited use of FUBCs. These findings did not differ between GPC and GNB bacteremia.

These data support that FUBCs may have little utility in the management of GNB bacteremia. In certain clinical settings, more FUBCs may not always lead to better patient care. In addition to cost-ineffectiveness, excessive FUBCs may lead to false positives, prompting further studies and possibly prolonged treatment courses and hospital stays. Previously proposed guidelines have suggested that FUBCs may be appropriate for new septic episodes, confirmation of intravenous catheter–associated bacteremia, diagnosis of suspected endocarditis, confirmation of response to therapy for endocarditis, and for therapeutic indications associated with *S. aureus* bacteremia [6].

There are currently no guidelines in place regarding the duration of treatment or use of FUBC for GNB infections. Even in GNB infections most prone to seeding the bloodstream, the bacteremia usually resolves within a short time after the

**Table 3. Differences Between Patients Whose Follow-up Blood Cultures Were Negative, or Positive for Gram-Positive Cocci and Gram-Negative Bacilli**

| Characteristic | Negative (n = 328) | | FUBC Positive for GPC (n = 43) | | *P* Value[a] | FUBC Positive for GNB (n = 8) | | *P* Value[a] |
|---|---|---|---|---|---|---|---|---|
| On antibiotics when cultures drawn | 312 | 95% | 42 | 98% | .71 | 8 | 100% | 1.00 |
| Medical disease (vs surgical) | 265 | 81% | 39 | 91% | .14 | 6 | 75% | .65 |
| Fever when cultures drawn | 100 | 30% | 21 | 49% | **.02** | 6 | 75% | **.01** |
| Presence of a urinary catheter | 82 | 25% | 9 | 21% | .71 | 1 | 13% | .69 |
| Presence of an IV central catheter | 121 | 37% | 27 | 63% | **.002** | 5 | 63% | .16 |
| Neutropenia (ANC < 1000/mL) | 29 | 9% | 3 | 7% | 1.00 | 1 | 13% | .53 |
| Diabetes mellitus | 121 | 37% | 23 | 53% | **.04** | 6 | 75% | .06 |
| HIV positive | 20 | 6% | 3 | 7% | .74 | 0 | 0% | 1.00 |
| ESRD on hemodialysis | 65 | 20% | 20 | 47% | **<.001** | 3 | 38% | .21 |
| Liver cirrhosis | 33 | 10% | 3 | 7% | <.78 | 2 | 25% | .20 |
| ICU care required | 119 | 36% | 12 | 28% | .31 | 4 | 50% | .47 |
| Death | 35 | 11% | 3 | 7% | .60 | 0 | 0% | .36 |

Data are presented as No. (%) unless otherwise indicated. Bold numbers represent those statistically significant.

Abbreviations: ESRD, end-stage renal disease; FUBC, follow-up blood culture; GNB, gram-negative bacilli; GPC, gram-positive cocci; HIV, human immunodeficiency virus; ICU, intensive care unit; IV, intravenous.

[a] *P* value for the difference vs negative FUBC.

**Table 4. Incidence of Bacteremia per Source (n = 273)**

| Characteristic | No. | Positive | | Negative | | *P* Value |
|---|---|---|---|---|---|---|
| Urinary tract infection | 71 | 2 | 3% | 69 | 97% | **.001** |
| Severe skin infection | 70 | 4 | 6% | 66 | 94% | **.026** |
| Intravenous catheter | 61 | 21 | 34% | 40 | 66% | **<.001** |
| Pneumonia | 34 | 5 | 15% | 29 | 85% | .79 |
| Intra-abdominal infection | 21 | 2 | 10% | 19 | 90% | .75 |
| Endocarditis | 6 | 1 | 17% | 5 | 83% | .59 |
| Osteomyelitis | 5 | 0 | 0% | 5 | 100% | 1.00 |
| Pleural empyema | 3 | 1 | 33% | 2 | 67% | .35 |
| Septic arthritis | 1 | 1 | 100% | 0 | 0% | .14 |
| Tonsillitis | 1 | 0 | 0% | 1 | 100% | 1.00 |

Data are presented as No. (%) unless otherwise indicated. Bold numbers represent those statistically significant.

institution of appropriate antibiotic therapy and/or source control [3]. Currently, the management of GNB bacteremia is determined by clinical judgment, allowing some clinicians to utilize blood cultures in an unrestricted way. Unrestrained use of blood cultures has serious implications for patient safety and healthcare costs. Unnecessary FUBCs have the potential to elicit false-positive results, which can have costly implications [7]. As many as 90% of all blood cultures grow no organisms [8]. Of the approximate 10% that do grow organisms, almost half are considered contaminants (false positives) [9]. Assuming a constant rate of contamination, the more FUBCs performed, the higher the chance of encountering contamination, which may result in increased costs, longer hospital stays, unnecessary consultations, and inappropriate use of antibiotics [7].

Our study has some limitations: First, we eliminated contaminants upfront, likely skewing the distribution of the true-positive cultures. Second, the medical records examined did not offer an explanation of why the FUBCs were ordered. That kind of explanation might open opportunities to educate physicians on the actual indication for blood cultures. Third, and related to the previous one, there is no explanation on whether a perception of disease severity played a role in the decision to obtain FUBCs only in 77% of our cohort, and not in all of it. Finally, the analysis of risk factors for positive GNB FUBCs is limited by the low incidence of such event.

In conclusion, FUBCs may not be indicated in the setting of GNB bloodstream infections. We caution physicians against drawing FUBCs in GNB bacteremia, as doing so might potentially lead to false-positive results, longer hospital stays, and higher healthcare costs.

## Note

***Potential conflicts of interest.*** All authors: No reported conflicts of interest. 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.

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