

# Risk Factors for Positive Follow-Up Blood Cultures in Gram-Negative Bacilli Bacteremia: Implications for Selecting Who Needs Follow-Up Blood Cultures

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**Background.** The value of follow-up blood cultures (FUBCs) to document clearance of bacteremia due to Gram-negative bacilli (GNB) has not been well established. Although previous studies suggested that the yield of FUBCs for GNB bacteremia is low, it remains to be elucidated for whom FUBC may be beneficial and for whom it is unnecessary.

**Methods.** A retrospective cohort study was performed at 4 acute care hospitals to identify risk factors for positive FUBCs with GNB bacteremia and to better guide clinicians' decisions as to which patients may or may not benefit from FUBCs. Participants included adult patients with GNB bacteremia who had FUBCs and were admitted between January 2017 and December 2018. The primary outcomes were the factors associated with positive FUBCs and the yield of FUBCs with and without the factors.

**Results.** Of 306 patients with GNB bacteremia who had FUBCs, 9.2% (95% confidence interval, 6.2%–13.0%) had the same GNB in FUBCs. In the multivariate logistic regression analysis, end-stage renal disease on hemodialysis, intravascular device, and bacteremia due to extended-spectrum  $\beta$ -lactamase or carbapenemase-producing organism were identified as independent predictors of positive FUBCs with GNB bacteremia. Approximately 7 FUBCs and 30 FUBCs were needed for patients with  $\geq 1$  or no risk factors, respectively, to yield 1 positive result.

**Conclusions.** Follow-up blood culture may not be necessary for all patients with GNB bacteremia and has the highest yield in patients with 1 or more risk factors.

**Keywords.** bacteremia; follow-up blood culture; Gram-negative bacilli.

The optimal duration of treatment for bloodstream infection due to Gram-negative bacilli (GNB) is yet to be determined [1]. Currently, the duration of antibiotic therapy for GNB bacteremia is mainly determined by clinical judgment, based on various factors such as the clinical response, the primary source of bacteremia, source control, and the immunological status [2].

Follow-up blood cultures (FUBCs) to document clearance of bloodstream infection are recommended for *Staphylococcus aureus* bacteremia [3] and for candidemia [4], and the exact duration of therapy is determined by the duration of bacteremia or fungemia. However, there is no such recommendation for bacteremia due to aerobic GNB. Although bacteremia due to aerobic

GNB can cause endovascular infection and persistent bacteremia in some situations, the routine utilization of FUBCs can be associated with increased resource utilizations, increased cost, false-positive results, and unnecessarily increased duration of antibiotic therapy [5, 6]; there are scant data directly addressing the issue of which patients with GNB bacteremia benefit most from FUBCs to document clearance of bloodstream infection and which patients with GNB bacteremia are unlikely to have positive FUBC with the same GNB and hence are not likely to need routine FUBCs.

A recent retrospective study found that the frequency of positive FUBCs performed after GNB bacteremia is lower than FUBCs performed after Gram-positive cocci (GPC) bacteremia, with yields of 6% and 21%, respectively [5]. However, the analysis of risk factors in this study for positive FUBCs with the same GNB bacteremia was limited due to the low incidence of the event [5]. Although there are some retrospective studies that analyzed risk factors for persistent bacteremia in patients with *Klebsiella pneumoniae* bacteremia [7] and bacteremia secondary to urinary tract infection [8], data are limited for other GNB organisms and other foci of infection. The present study aimed to identify risk factors for the presence of positive FUBC with the same GNB bacteremia and to identify the yield of FUBCs in patients with and without specific risk factors.

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## METHODS

### Study Design and Patient Population

A retrospective, multicenter observational study was performed at Mount Sinai Beth Israel, Mount Sinai West, Mount Sinai St. Luke's, and Mount Sinai Brooklyn, all of which are acute care hospitals in New York City. Adult patients who were admitted between January 2017 and December 2018 with GNB bacteremia were eligible for the study. Patients were excluded if they were younger than 18 years of age or if the initial positive blood culture was considered contamination by treating medical providers. Study approval was obtained from the institutional review board of the Icahn School of Medicine at Mount Sinai.

### Data Collection and Analysis

We obtained a list of all patients with  $\geq 1$  blood cultures positive for GNB during the study period and reviewed electronic medical records to identify those patients who met the inclusion criteria. We collected the following data: age, gender, body mass index, organisms isolated from blood cultures and their antimicrobial susceptibilities, presumed source of bacteremia, intensive care unit (ICU) stay between the initial blood cultures and the FUBCs, antibiotics given at the time of FUBC, presence of fever at the time of FUBC, comorbidities including neutropenia, human immunodeficiency virus infection, diabetes mellitus, end-stage renal disease (ESRD) on hemodialysis, liver cirrhosis, vasopressor use, mechanical ventilator use, presence of central lines and intravascular devices, length of stay, and in-hospital mortality. We also extracted the laboratory data from the time of initial blood culture, including white blood cell count, lactate, and creatinine.

### Definitions

#### Positive Follow-Up Blood Cultures

Positive FUBC is defined as bacteremia in which the FUBCs grew the same organism as the initial blood culture, as long as the FUBC was obtained at least 24 hours after the initial blood culture. Any positive blood cultures drawn within 24 hours of the initial positive culture were considered as the same episode. The threshold of at least 24 hours was chosen to be consistent with that used in Canzoneri et al [5]. Only the first FUBC was examined in analyses.

#### Neutropenia

Neutropenia was defined as an absolute neutrophil count less than 1000 cells per microliter at the time of the initial blood culture.

#### Fever

Patients were considered febrile if their body temperature recorded was  $\geq 100.4$  ( $38^\circ\text{C}$ ) on the day of FUBCs.

#### Intravascular Device

Intravascular device is defined as a central line (conventional central venous catheter, peripherally inserted central catheter,

tunneled catheter, and/or implanted port) and any other vascular device including implantable cardiac defibrillators, pacemakers, prosthetic valves, and vascular grafts.

### Source Control

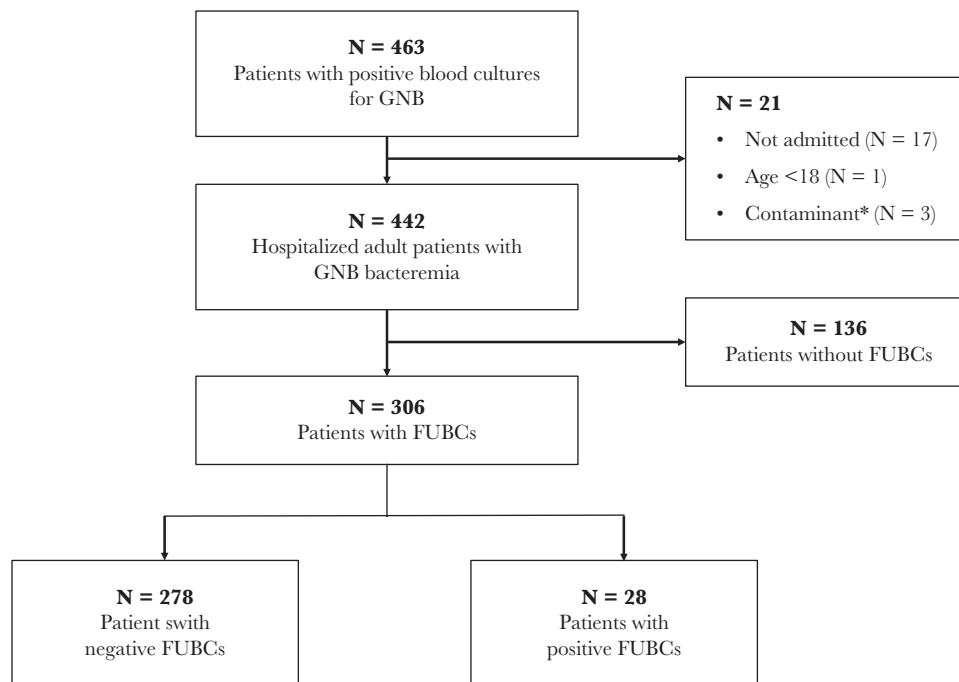
Source control is defined as any procedure performed to control the source of the bacteremia after the initial blood culture. We did not include exchange of indwelling urinary catheters due to relatively sparse documentation in medical charts compared with that for other source control measures.

### Statistical Analysis

Fisher exact tests were used to compare categorical variables. Mann-Whitney  $U$  tests were used to compare continuous variables. We performed a multivariate logistic regression analysis to identify risk factors for positive FUBC with the same GNB bacteremia. Age, gender, and variables with  $P < .10$  in the univariable analysis were included in the multivariate analysis. These variables were examined for correlation before inclusion in the multivariate analysis. Finally, we calculated the yield of FUBCs by dividing the number of cases found to have positive FUBCs by the number of total episodes of GNB bacteremia that had FUBCs performed. We identified the yields of FUBCs in all patients with FUBCs, and we compared the yields in patients with or without any of the independent risk factors that were identified in the multivariate analysis. A 2-sided  $P < .05$  was considered statistically significant. All statistical analyses were conducted using R commander, a graphical user interface for R (version 3.6.1; The R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

There were a total of 463 patients with blood cultures that grew GNB during the study period. Of these, 306 (66%) had FUBCs performed at least once (Figure 1). The organisms isolated in the initial blood cultures were as follows: *Escherichia coli* (154), *K pneumoniae* (65), *Proteus mirabilis* (35), *Enterobacter cloacae* (18), *Pseudomonas aeruginosa* (14), *Morganella morganii* (10), *Acinetobacter baumannii* (7), *Haemophilus influenzae* (6), *Providencia stuartii* (5), *Serratia marcescens* (4), *Bacteroides fragilis* (4), *Fusobacterium necrophorum* (3), *Hafnia alvei* (3), *Klebsiella oxytoca* (3), nontyphoidal *Salmonella* spp (3), *Stenotrophomonas maltophilia* (3), *Bacteroides thetaiotaomicron* (2), and others (22); each organism was isolated only once. The FUBCs were obtained a median of 2 days (interquartile range, 1–4 days) after the initial blood culture. All study patients except 2 were receiving antibiotics active against GNB between the time of the initial blood culture and the respective FUBC. Of these 2, one received only vancomycin in the interval between the initial blood culture and FUBC, and the FUBC was positive for *F necrophorum* and *Streptococcus sanguinis* (the same organisms with the initial blood culture); the other received only



**Figure 1.** The graphic illustrates the patient selection flow. \*, The 3 patients had the initial positive blood culture, which were considered contaminants and were not treated by providers. The organisms were as follows: *Brevundimonas diminuta* isolated along with *Micrococcus* spp; *Pseudomonas putida* and *Acinetobacter baumannii*; Gram-negative bacilli, Gram-positive cocci in pair; and Gram positive cocci in chains, for which no further microbial evaluation was performed. GNB, Gram-negative bacilli; FUBC, follow-up blood culture.

linezolid in the interval between the initial blood culture and FUBC and the FUBC was negative.

Of the 306 patients with FUBCs, 28 (9.2%; 95% binomial confidence interval [CI], 6.2%–13%) had positive FUBCs with the same GNB. The FUBCs were positive for *E coli* (10), *K pneumoniae* (8), *E cloacae* (1), *P aeruginosa* (2), *S marcescens* (2), *S maltophilia* (2), *F necrophorum* (1), *M morgani* (1), and *Salmonella dublin* (1).

Characteristics of the patients with FUBCs and univariate factors associated with positive FUBCs are described in Table 1. Patients with positive FUBCs with the same GNB were significantly more likely to (1) be in the ICU (64% vs 40%,  $P = .02$ ), (2) have ESRD on hemodialysis (36% vs 13%,  $P = .004$ ) and intravascular device (64% vs 33%,  $P = .002$ ) as comorbidities, (3) have central-line associated bloodstream infection ([CLABSI] 18% vs 4%,  $P = .01$ ) as the source of infection, and (4) have extended-spectrum  $\beta$ -lactamase (ESBL) or carbapenemase-producing organisms as the cause of bacteremia (32% vs 16%,  $P = .04$ ), compared with patients with negative FUBC. There was no significant difference in length of hospital stay and in-hospital mortality between the groups.

The result of the multivariate logistic regression analysis is presented in Table 2. Among the variables with  $P < .10$  in the univariable analysis, CLABSI and intravascular device were highly correlated with each other. We included only intravascular device as a potential risk factor in the multivariate analysis because it is a more inclusive variable (all patients with

CLABSI had an intravascular device by definition) and the presence of an intravascular device is known before the diagnosis of a CLABSI, and hence it is a more readily available factor to inform whether to obtain an FUBC. Factors independently associated with positive FUBC with the same GNB were ESRD on hemodialysis (adjusted odds ratio [aOR], 2.95; 95% confidence interval [CI], 1.14–7.61), intravascular device (aOR, 2.52; 95% CI, 1.02–6.28), and ESBL or carbapenem-producing organism (aOR, 3.07; 95% CI, 1.22–7.76). Variance inflation factors (VIFs) were less than 2 in the multivariate regression model (data not shown).

The yield of FUBCs in patients with  $\geq 1$  of the factors found to be independently associated with positive FUBCs identified in the multivariate analysis (ie, patients with ESRD on hemodialysis, intravascular devices, and/or ESBL or carbapenem-producing organisms) was 23 of 155 episodes (14.8%; 95% CI, 9.7%–21.4%). In contrast, the yield of FUBCs in patients without any of the risk factors was 5 of 151 episodes (3.3%; 95% CI, 1.1%–7.6%). Those with no risk factors were significantly less likely to have a positive FUBC than those with 1 or more risk factors (3.3% vs 14.8%,  $P = .0014$ ). These results indicate that approximately 7 FUBCs were needed to yield 1 positive result in patients with  $\geq 1$  risk factors; however, 30 FUBCs were needed in patients without the risk factors. Had routine FUBCs been limited to those with  $\geq 1$  risk factor, positive FUBCs would have been undetected in 5 of 306 patients (1.6%). The yields of FUBCs are presented in Table 3.

**Table 1. Patient Characteristics<sup>a</sup>**

Characteristic	Negative FUBC	Positive FUBC	P Value
	(N = 278)	(N = 28)	
Age, years, median (IQR)	69.5 (59.0–83.0)	65.5 (57.0–77.3)	.25
Male sex	149 (54)	16 (57)	.84
BMI, median (IQR)	26.5 (22.5–31.7)	26.5 (23.0–29.6)	.97
Interval days between the initial and follow-up blood culture, median (IQR)	2.5 (1.0–4.0)	2.0 (2.0–3.0)	.14
ICU level of care	112 (40)	18 (64)	<b>.02</b>
Vasopressor support	63 (23)	8 (29)	.49
Ventilatory support	63 (23)	9 (32)	.25
White blood cells ( $\times 10^3/\mu\text{L}$ ), median (IQR)	13.7 (8.6–20.5)	12.4 (11.0–18.2)	.85
Lactate (mmol/L), median (IQR)	2.6 (1.8–4.0)	2.8 (1.3–4.7)	.97
Creatinine (mg/dL), median (IQR)	1.4 (1.0–2.7)	1.8 (0.8–3.9)	.52
Neutropenia (ANC <1000/mL)	7 (3)	0 (0)	1.00
HIV infection	15 (5)	1 (4)	1.00
Diabetes mellitus	118 (42)	10 (36)	.55
ESRD on hemodialysis	36 (13)	10 (36)	<b>.004</b>
Cirrhosis	9 (3)	1 (4)	1.00
Intravascular device	91 (33)	18 (64)	<b>.002</b>
Presumed source of bacteremia			
Unclear source	46 (17)	5 (18)	.86
Urinary tract infection	116 (42)	11 (39)	.80
Pneumonia	12 (4)	2 (7)	.50
Skin and soft tissue infection	19 (7)	0 (0.0)	.15
CLABSI	10 (4)	5 (18)	<b>.01</b>
Endovascular infection	3 (1)	0 (0)	.58
Intra-abdominal infection	23 (8)	1 (4)	.38
Hepatobiliary infection	34 (12)	3 (11)	.81
Osteomyelitis	14 (5)	1 (4)	.73
Other	1 (0)	0 (0)	.75
Polymicrobial infection	65 (23)	7 (25)	.82
ESBL or carbapenemase-producing organism	44 (16)	9 (32)	<b>.04</b>
Fever	55 (20)	7 (25)	.62
Source control performed	98 (35)	11 (39)	.68
Length of hospital stay, median (IQR)	10.0 (6.0–17.0)	12.5 (8.00–20.8)	.11
In-hospital mortality	25 (9)	3 (11)	.73

Abbreviations: ANC, absolute neutrophil count; BMI, body mass index; CLABSI, central line-associated bloodstream infection; ESBL, extended-spectrum  $\beta$ -lactamase; ESRD, end-stage renal disease; FUBC, follow-up blood culture; HIV, human immunodeficiency virus; ICU, intensive care unit; IQR, interquartile range.

<sup>a</sup>Data are presented as number (%) unless indicated otherwise. Statistically significant numbers were highlighted in boldface type.

## DISCUSSION

In our multisite retrospective cohort study, approximately two thirds of the hospitalized adult patients with GNB bacteremia had FUBCs performed. Of those, less than 10% of patients had

positive FUBCs with the same GNB identified. The multivariate logistic regression analysis identified ESRD, intravascular device, and bacteremia due to ESBL or carbapenemase-producing organism as independent predictors for positive FUBC with the same GNB. The yield of FUBCs in those with GNB bacteremia and with risk factors was almost 15%, a rate that supports the practice of FUBC in this setting. On the other hand, the yield of FUBCs with GNB bacteremia and none of the examined and identified risk factors was only 3.3%, and in this cohort limiting FUBCs to those with risk factors would have failed to identify 1.6% (5 of 306) of cases, suggesting that routine FUBCs in the absence of risk factors may not be needed.

The yield of FUBCs in our cohort was 9.2% (95% CI, 6.2%–13%), which was comparable to that identified in the only previous study (conducted by Canzoneri et al [5]) addressing this issue (5.7% [95% CI, 2.5%–10.9%] in 140 episodes of GNB

**Table 2. Factors Independently Associated With Positive Follow-Up Blood Culture for Gram-Negative Bacilli Bacteremia<sup>a</sup>**

Variable	Adjusted OR (95% CI)	P Value
ESRD on hemodialysis	2.95 (1.14–7.61)	<b>.025</b>
Intravascular device	2.52 (1.02–6.28)	<b>.046</b>
ESBL or carbapenemase-producing organism	3.07 (1.22–7.76)	<b>.018</b>

Abbreviations: CI, confidence interval; ESBL, extended-spectrum  $\beta$ -lactamase; ESRD, end-stage renal disease; OR, odds ratio.

<sup>a</sup>Statistically significant numbers were highlighted in boldface type.

**Table 3. The Yield of Follow-Up Blood Cultures<sup>a</sup>**

	Total	Positive FUBC	The Yield of FUBC (%) (95% CI)	P Value
All patients with FUBC	306	28	9.2 (6.2–13.0)	–
Patients with ≥1 risk factors	155	23	14.8 (9.7–21.4)	–
Patients with no risk factors	151	5	3.3 (1.1–7.6)	<b>.001</b>

Abbreviations: CI, confidence interval; ESBL, extended-spectrum β-lactamase; ESRD, end-stage renal disease; FUBC, follow-up blood culture.

<sup>a</sup>Risk factors: ESRD on hemodialysis, intravascular device, and ESBL or carbapenem-producing organism.

bacteremia). One possible explanation for the slightly higher yield in our study is that we included only the first FUBC for each episode of bacteremia, whereas the previous study included all FUBCs drawn for each episode. Gram-negative bacilli bacteremia is usually transient in the absence of infected intravascular bioprosthetic material, and it is clinically plausible that FUBCs drawn after the institution of appropriate antibiotic therapy are more likely to be negative. It is unlikely that our cohort represented a sicker population based on ICU admission rate and in-hospital mortality compared with that in Canzoneri et al [5].

Few previous studies assessed factors predictive of persistent GNB bacteremia, and the findings are not fully consistent. For *K pneumoniae* bacteremia, a retrospective case-control study from Korea found that intra-abdominal infection, higher Charlson's comorbidity weighted index score, history of solid organ transplantation, and unfavorable treatment response were independent risk factors [7]. For bacteremic urinary tract infection, malignancy, ICU admission, high C-reactive protein (CRP) level, and a time to defervescence >48 hours were suggested by another retrospective study from Korea. In our cohort, fever on the day of FUBC was not significantly associated with positive FUBC. It has been repeatedly reported that fever and leukocytosis do not strongly predict persistent bacteremia because they are nonspecific and can be elevated due to noninfectious causes [9, 10]. C-reactive protein was not measured in most of our cases.

In our study, ESRD may be a surrogate for more severely ill patients in general or may reflect impaired immune function in patients with ESRD. It is also possible that either “ESRD on hemodialysis” or “having an intravascular device” may be confounders or effect modifiers; however, multicollinearity was considered unlikely because all of the VIFs were less than 2 in the multivariate regression model. The association with positive FUBC and intravascular devices likely reflects cases in which antibiotic therapy alone was insufficient to clear bacteremia because of organisms adherent to the biofilm of catheters and

which therefore required source control including exchange or removal of the central venous catheter or some other devices; it has been generally empirically accepted that CLABSI requires FUBC to document clearance and determine treatment duration from the first negative culture [6]. This is also consistent with the results of a case-control analysis that found that *S aureus* bacteremia or endovascular infection including CLABSI were risk factors of persistent bacteremia in patients with GPC or GNB bacteremia [11].

It is biologically plausible that the finding of an association of multidrug-resistant GNB with positive FUBC was related to the fact that in many cases of bacteremia due to ESBL or carbapenemase-producing organisms, the patients received initial empirical antimicrobial therapy (eg, cephalosporins and β-lactam/β-lactamase inhibitors) that was not effective against the isolated organisms. It has been previously shown that treatment with an antibiotic ineffective against ESBL-producing *K pneumoniae* is associated with treatment failure and increased mortality [12, 13]. Some ESBL-producing GNB may be found to be susceptible to cefepime and piperacillin-tazobactam in vitro, but it is known that carbapenems are superior to cephalosporins or β-lactam/β-lactamase inhibitors for bacteremia with ESBL-producing GNB [12, 14]. Our data suggest that routine repeat blood cultures may be appropriate to document clearance of bloodstream infection due to multidrug-resistant GNB, especially in settings in which the initial empiric therapy of multidrug-resistant GNB bacteremia may have been ineffective.

Currently, there is no clinical practice guideline on FUBC for GNB bacteremia. Because the decision upon FUBC for GNB bacteremia depends solely on clinical judgment, FUBC may have been liberally utilized without support from good evidence. Moreover, there seems to be substantial practice variation. For example, 69% of the patients had at least 1 FUBC in our cohort; 32% in Tabriz et al [15]; 39% in Wiggers et al [11]; 77% in Canzoneri et al [5]; 81% in Kang et al [7]; and 92% in Shi et al [8]. The results of our study revealed that the yield of FUBC was very low in patients without certain risk factors. The result is consistent with a recent study that showed that the sensitivity of blood cultures is significantly reduced shortly after initiation of empirical antimicrobial therapy in patients with sepsis [16]. In addition, routine FUBCs rarely isolate new pathogens in patients receiving antimicrobial therapy [17]. On the other hand, the yield of FUBC for GNB bacteremia in patients with 1 or more of the predictive factors identified in this study (14.8%; 95% CI, 9.7%–21.4%) may be comparable to that of FUBCs done in the setting of GPC bacteremia (20.8% in Canzoneri et al [5] and 19.6% in Wiggers et al [11]). The yield of FUBCs after GNB bacteremia may be enhanced, and the number and proportion of negative and potentially contaminated FUBCs may be reduced by focusing FUBC efforts on patients with the identified risk factors; as a consequence, patient inconvenience, clinical staff effort and laboratory volume, the risk of false-positive

blood cultures leading to prolonged antibiotic therapy, and the length of stay could possibly be reduced [6, 18].

This study has several limitations. First, in our population of adult patients hospitalized with GNB bacteremia, 30.7 % (136 of 442) did not have FUBC. The rationale for the decision to perform an FUBC in each individual case was not well documented in the medical records. Second, there may have been potential confounding factors that were not measured due to the retrospective study design. In addition, although patients with a urinary focus represented a large group within the study population, available medical record documentation precluded an examination of the impact of urinary catheter exchanges as source control. Furthermore, because the number of FUBCs any individual received was not standardized, our analyses of the results of the first FUBC could theoretically under reflect situations in which patents remained bacteremic intermittently. Data on bilirubin and CRP were not collected to allow a calculation of a Sequential Organ Failure Assessment (SOFA) score and a correlation between inflammatory markers and positive FUBC, respectively, given the expectation of a high rate of missing values of these tests. Finally, the multivariate analysis may be limited by the low incidence of positive FUBCs. For example, the ICU level of care might have been a significant risk factor if the sample size was larger. A prospective validation study is warranted to evaluate the generalizability of the risk factors for positive FUBCs identified in this study.

## CONCLUSIONS

In conclusion, ESRD on hemodialysis, intravascular devices, and bacteremia due to multidrug-resistant GNB were independently associated with positive FUBC in patients with GNB bacteremia. Our findings suggest that FUBC may not be necessary for all patients with GNB bacteremia and has the highest yield in patients with 1 or more risk factors.

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