Journal of Community Hospital Internal Medicine Perspectives

Volume 12 | Issue 6 Article 6

2022

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Azza Elamin
Department of Internal Medicine, Division of Infectious Diseases, Trinity Health St. Joseph Mercy Hospital Ann Arbor

Faisal Khan
Department of Internal Medicine, Division of Infectious Diseases, Trinity Health St. Joseph Mercy Hospital Ann Arbor, faisal.khan001@stjoeshealth.org

Rajasekhar Jagarlamudi
Department of Internal Medicine, Division of Infectious Diseases, Trinity Health St. Joseph Mercy Hospital Ann Arbor

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Elamin, Azza; Khan, Faisal; and Jagarlamudi, Rajasekhar (2022) "Follow-up blood cultures in Gram-negative bacteremia: How do they impact outcomes?," *Journal of Community Hospital Internal Medicine Perspectives*: Vol. 12: Iss. 6, Article 6.
DOI: 10.55729/2000-9666.1131
Available at: https://scholarlycommons.gbmc.org/jchimp/vol12/iss6/6

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Follow-up Blood Cultures in Gram-negative Bacteremia: How Do They Impact Outcomes?

Azza Elamin, Faisal Khan*, Rajasekhar Jagarlamudi

Department of Internal Medicine, Division of Infectious Diseases, Trinity Health St. Joseph Mercy Hospital Ann Arbor, MI, USA

Abstract

Introduction: **Several studies have questioned the utility of obtaining follow-up blood cultures in Gram-negative bacteremia, but the impact of this practice on clinical outcomes is not fully understood.**

Methods: **A retrospective cohort study of adult patients admitted with Gram-negative bacteremia over a two year period, to compare outcomes in those with and without follow-up blood cultures obtained. Data collected included demographics, comorbidities and presumed source of bacteremia. White blood cell count and presence of fever or hemodynamic compromise on the day of follow-up blood culture were recorded. The primary objective was to compare 30-day mortality between the two groups. Secondary objectives included comparing 30-day readmission rate, hospital length of stay and antibiotics duration.**

Results: **Of 482 included patients, 321 (66.6%) had follow-up blood cultures. 96% of follow-up blood cultures were negative. Persistent bacteremia occurred in 9 patients. There was no significant difference in 30-day mortality between those with and without follow-up blood cultures (2.9% and 2.7% respectively, $P > 0.999$), and no difference in 30-day readmission rate (21.4% and 23.4% respectively, $P = 0.704$). Patients with follow-up blood cultures had longer hospital length of stay (7 days vs 5 days, $P < 0.001$), and longer mean antibiotic duration (14 days vs 11 days, $P < 0.001$).**

Conclusion: **Obtaining follow-up blood cultures in Gram-negative bacteremia had no impact on 30-day mortality or 30-day readmission rates. It was associated with longer length of stay and antibiotic duration. We found this practice to be low yield and its routine use may be of questionable value.**

Keywords: Gram-negative bacteremia, Follow-up blood cultures, Clinical outcomes, 30-day mortality

1. Introduction

In recent decades, Gram-negative (GN) pathogens have been surpassed by Gram-positive pathogens as the most common causes of blood stream infections (BSI).[1] Several studies however have shown the reemergence of GN pathogens as important causes of BSI in both healthcare and community settings.[2,3,4] One study reported 45% of community onset and 31% of nosocomial BSI to be secondary to GN pathogens.[2] Of particular concern is the emergence of drug resistance among GN pathogens thereby posing serious treatment challenges and leading to worse outcomes.[5,6,7,8]

As opposed to *Staphylococcus aureus* bacteremia where follow-up blood cultures (FUBCs) to document clearance of bacteremia are indicated,[9] no similar guidelines exist for repeating blood cultures in Gram-negative bacilli bacteremia (GNB). In fact, some studies have questioned the utility of such practice in GNB.[10,11,12] Blood cultures are frequently low yield leading to unnecessary increases in healthcare costs and hospital length of stay (LOS).[13,14,15] As such, they should be judiciously used as clinically warranted.

Our aim was to study the practice of collecting FUBCs in GNB at our institution and to assess if this had any impact on clinical outcomes such as 30-day mortality, 30-day readmission rate, duration of antibiotic use, need for Intensive Care Unit (ICU) stay and overall hospital length of stay (LOS).

Received 11 July 2022; revised 24 August 2022; accepted 31 August 2022.
Available online 7 November 2022

* Corresponding author at: 5333 McAuley Dr Suite 5011, Ypsilanti, MI, 48197, USA. Fax: +734 712 5583.
E-mail address: azzaamin39@gmail.com (A. Elamin), Faisal.Khan001@stjoeshealth.org (F. Khan), rajjagarlamudi@gmail.com (R. Jagarlamudi).

https://doi.org/10.55729/2000-9666.1131
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2. Methods

2.1. Study design and patient population

A retrospective single-center study was performed at Trinity Health St. Joseph Mercy Hospital Ann Arbor, Michigan (SJMAA). Patients eligible for the study included those ≥18 years of age, admitted to SJMAA between January 1, 2017 and December 31, 2018, with GNB. Patients were excluded if they 1) died within 24 h of admission or of the index blood culture, whichever came first; 2) refused antibiotic therapy or did not complete the recommended course of therapy; or 3) were transitioned to comfort care/hospice before completing the recommended antibiotic course for that episode of bacteremia at any point during their hospitalization. We divided the cohort into two groups: those with at least one FUBC obtained, and those without any FUBCs collected. Our primary objective was to compare 30-day mortality between the two groups. Our secondary outcomes included differences in 30-day readmission rate, hospital LOS and antibiotics duration between the two groups. The percentages of patients that required ICU admission were compared as well. The study was approved by the hospital's Institutional Review Board and Ethics Committee.

2.2. Data collection and analysis

We reviewed the electronic medical records (EMR) of all episodes of GNB, and collected data for those patients eligible for inclusion, using REDCap software (Vanderbilt University, Nashville, TN). Data was collected for baseline characteristics, including age and sex. We collected data for comorbid conditions and risk factors including diabetes, hypertension, congestive heart failure, ischemic heart disease, peripheral arterial disease, impaired liver function, end-stage renal disease (ESRD), immunosuppressive therapy (systemic corticosteroids, chemotherapeutic agents, and biologic agents), neutropenia (defined as absolute neutrophil count <1000 cells/microL), presence of indwelling central venous catheters, urinary tract catheters/tubes, and/or prosthetic heart valves. Data collected specific to blood cultures included: organism(s) isolated from the index and follow-up blood culture(s), presumed source of bacteremia, empiric antibiotic therapy at the time of collection of index blood cultures, antibiotic susceptibilities, number of FUBCs obtained, and reason for obtaining FUBCs if it was documented in the medical chart. White blood cell (WBC) count and presence of fever or hemodynamic compromise on the day of FUBCs were recorded as well.

2.3. Definitions

Index blood culture: The first blood culture associated with clinically significant GNB that occurred for a patient during the study period.

Follow-up blood culture(s) (FUBCs): Blood culture(s) obtained after 24 h and within 7 days from the index blood culture. Blood cultures obtained within 24 h were considered as part of the index bacteremia. Any cultures obtained >7 days after the index culture were not considered FUBCs for the purpose of this study, and they were deemed a separate episode.

Persistent bacteremia: Any FUBC drawn in the >24 h and <7 day window, if growing the same organism(s) as the index blood culture.

Hospital-acquired infection: Clinically significant Gram-negative bacteremia developing after at least 48 h of hospital admission.

2.4. Statistical analysis

Mean and standard deviations were used to present continuous variables, whereas frequency and proportion were used for categorical variables. These statistics were calculated separately for the two groups, and balance between the groups was tested. We used t-tests to determine *P*-values for continuous variables; Fisher's exact test and χ^2-tests for categorical variables. Outcomes were tested using Mann–Whitney U and χ^2-tests. All statistical tests were 2-sided and a *P*-value <0.05 was defined as statistically significant. All statistical analysis was performed using the software environment R v4.0.0 (R Foundation, Vienna, Austria).

3. Results

There was a total of 584 cases of GNB, of which 102 cases were excluded (50 were transitioned to comfort care, 29 did not complete recommended course of antibiotic therapy and 23 died within 24 h of admission or of the index blood culture). The remaining 482 were divided into the two groups: 321 (66.6%) were those with FUBCs collected; and 161 (33.4%) were those without FUBCs collected (Fig. 1). There was no statistically significant difference in baseline characteristics, including demographics and comorbid conditions between the two groups (Table 1). The presumed source of bacteremia was similar in the two groups with urinary tract infection being the most common source (54.2% in the FUBCs

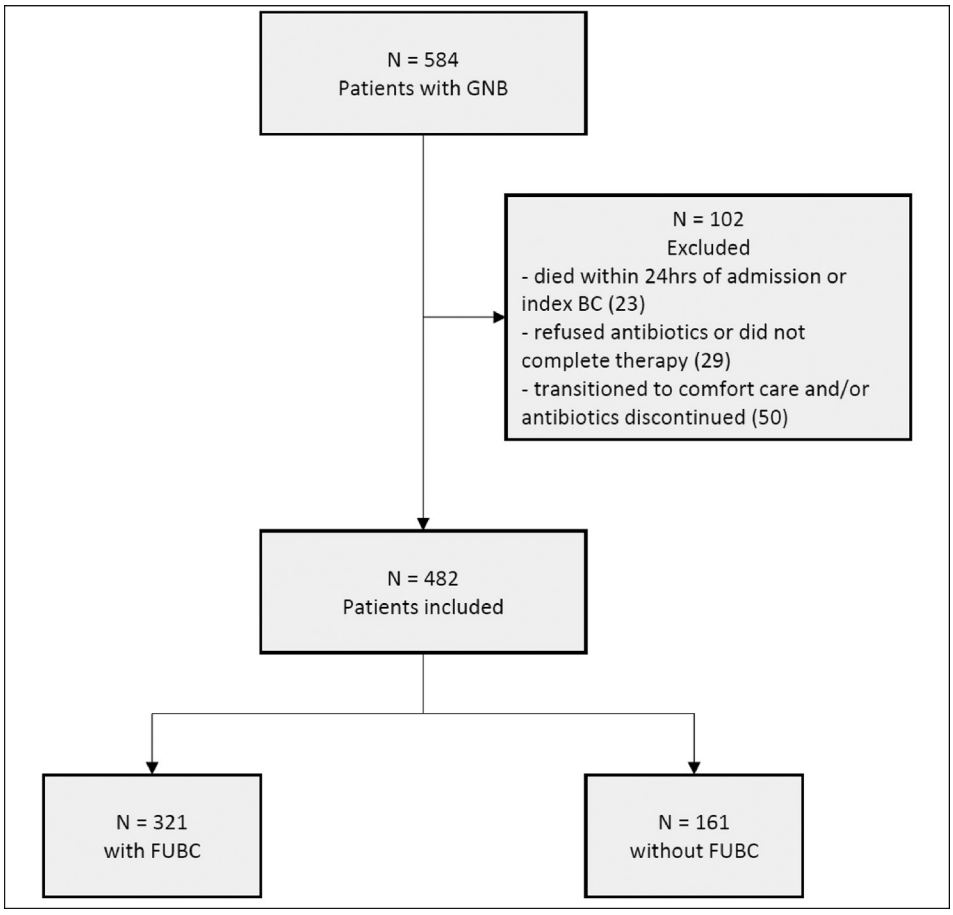

Fig. 1. Study Flow Diagram. Medical charts of 584 patients with GNB were reviewed, of which 102 were excluded. Of the 482 included patients, 321 patients had FUBCs and 161 patients did not. Abbreviations: N, number; GNB, Gram-negative bacteremia; BC, blood culture; FUBC, follow-up blood culture.

Table 1. Baseline characteristics.

Variable	with FUBCs (N = 321)	Without FUBCs (N = 161)	*P*-value
Age	69.4 (14.8)	70.2 (14.8)	0.603
Sex			>0.999
Female	163 (50.8%)	82 (50.9%)	
Male	158 (49.2%)	79 (49.1%)	
Current smoker	44 (14.3%)	16 (10.5%)	0.316
Presumed source			
UTI	174 (54.2%)	86 (53.4%)	0.946
Intra-abdominal infection	61 (19.0%)	24 (14.9%)	0.324
Severe skin/soft tissue infection	14 (4.6%)	5 (3.1%)	0.674
Other	24 (7.5%)	10 (6.2%)	0.747
No source identified	50 (15.6%)	35 (21.7%)	0.122
Hospital-acquired infection	40 (12.5%)	15 (9.4%)	0.395
Comorbid condition/Risk factor			
Diabetes mellitus	106 (33.0%)	53 (32.9%)	>0.999
Hypertension	175 (54.5%)	94 (58.4%)	0.478
Congestive heart failure	55 (17.1%)	28 (17.4%)	>0.999
Ischemic heart disease	51 (15.9%)	20 (12.4%)	0.381
Peripheral arterial disease	14 (4.4%)	8 (5.0%)	0.944
Impaired liver function	14 (4.4%)	6 (3.7%)	0.93
ESRD	21 (6.5%)	10 (6.2%)	>0.999
Immunosuppression/steroids/chemotherapy	42 (13.1%)	20 (12.4%)	0.952
Neutropenia	11 (3.4%)	6 (3.7%)	>0.999
Indwelling central line	17 (5.3%)	9 (5.6%)	>0.999
Bladder catheter and/or nephrostomy tube	35 (10.9%)	13 (8.1%)	0.414
Prosthetic Heart Valve	4 (1.3%)	1 (0.6%)	0.669

Abbreviations: FUBCs, follow-up blood cultures; N, number; UTI, urinary tract infection; ESRD, end-stage renal disease.
Note: *P*-values come from t-tests, χ^2-tests, and Fisher's exact tests depending on the distribution of the variable.

group and 53.4% in the no FUBCs group, $P = 0.946$) (Table 1). *Escherichia coli (E. coli)* was the causative organism in at least half the cases of bacteremia within each group (51% in those with FUBCs, and 53% in those without). Other organisms had similar distribution between the two groups as well (Fig. 2).

There was no significant difference in the primary outcome of 30-day mortality between those with FUBCs and those without (2.9% and 2.7% respectively; $P > 0.999$). However, the hospital LOS and duration of antibiotics were noted to be significantly different between the two groups. The mean length of stay was 7 days (IQR 5-11) for those with FUBCs and 5 days (IQR 4-7) for those without FUBCs ($P < 0.001$). The duration of antibiotic therapy was 14 days (IQR 10-14) in those with FUBCs, and 11 days (IQR 10-14) in those without FUBCs ($P < 0.001$). There was no statistically significant difference in 30-day readmission rate between the two groups, 21.4% in those with FUBCs and 23.4% in those without FUBCs ($P = 0.704$). Patients with FUBCs obtained were more likely to have needed intensive care during their hospitalization, 133 (41.4%) compared to 41 (25.5%) in patients without FUBCs obtained ($P < 0.001$) (Table 2).

We noted that in our study the vast majority of FUBCs (96%) were negative. Of those that were positive, 9 (2.8%) showed persistent bacteremia, a new pathogen was isolated in 2 patients (0.6%) and a contaminant was isolated in 1 patient (0.3%). A reason for obtaining FUBCs was recorded in the electronic medical record in 91 cases (28.5%), and of those the predominant reason was to document clearance of bacteremia (69 patients, 75.8%). We also collected data for clinicopathologic variables for all cases of FUBCs on the day they were obtained. On the day of FUBCs, 47 patients (14.6%) had a temperature >100.3 °F, 22 patients (6.9%) had hypotension (systolic blood pressure <90 mm Hg) or were on vasopressors and the mean WBC count was 12 (±6.74). The characteristics of the FUBCs are shown in Table 3.

4. Discussion

To our knowledge, this is the first study to assess 30-day mortality exclusively in patients who had FUBCs in GNB. There are no clear guidelines recommending repeat blood cultures in GNB and the impact of this practice on clinical outcomes is not fully understood. Our study showed no significant difference in 30-day mortality between those with or without FUBCs obtained for GNB. There was no significant difference in 30-day readmission rate between the two groups. The group with FUBCs however had longer hospital LOS and longer duration of antibiotic therapy. More patients in the FUBCs group were noted to require ICU admission.

Of 482 patients with GNB, 321 (66.6%) had FUBCs, however the yield was low with 96% being negative and only 2.8% showing persistent bacteremia with the same pathogen. Our findings are in keeping with those of Canzoneri et al. with persistent GNB found in only 6% of their cases.[10] Similarly, Wiggers et al. reported low yield for most repeat blood cultures in GNB after 48 h even though their proportion of cases with persistent GNB was higher (27 out of 220 patients had persistent bacteremia).[11] In another study of FUBCs in cases of *Klebsiella pneumoniae* bacteremia, 7.2% were found to have persistent bacteremia. The authors suggested a score of clinical and laboratory factors for predicting persistent *K. pneumoniae* bacteremia and concluded that routine FUBCs may not be justified.[12] An important difference is that in our study, over half of the patients had *E. coli* bacteremia which is slightly higher than what is reported in other studies.[2,5] Wiggers et al. found *E. coli* to be a rare cause of persistent bacteremia[11] which may explain at least in part our low positivity rate.

The positive predictive value of blood cultures in general can be as low as 58.3% due to the isolation of contaminants resulting in false positive results.[13] The possibility of isolating contaminants leads to increased LOS, and higher costs due to continued use of intravenous antibiotics and further microbiological testing.[15] In our study, a contaminant was isolated in only one patient in the FUBCs group which is unlikely to explain the longer hospital LOS in this group. In addition, excessive ordering of blood cultures can lead to unjustified increases in healthcare costs.[14,15]

Physicians are often prompted to obtain blood cultures as a response to deterioration in clinical status or laboratory abnormalities. In our study, the reason for repeating blood cultures was documented in the medical chart for only 91 patients (28.5%). Of those, 75.8% were obtained to confirm clearance, 19.8% for fever, and 4.4% for abnormal laboratory markers such as leukocytosis or high lactate. Of all those who had FUBCs whether or not a reason was documented, 14.6% were febrile, 6.9% were hypotensive and/or on vasopressors, and the average WBC count was 12 on the day of FUBCs. Physicians should be mindful of the fact that isolated fever or leukocytosis are poor predictors of blood culture positivity, and that pretest probability should be taken into consideration before ordering blood cultures.[16,17,18] 41.4% of patients in the FUBCs group needed ICU care at some point during their

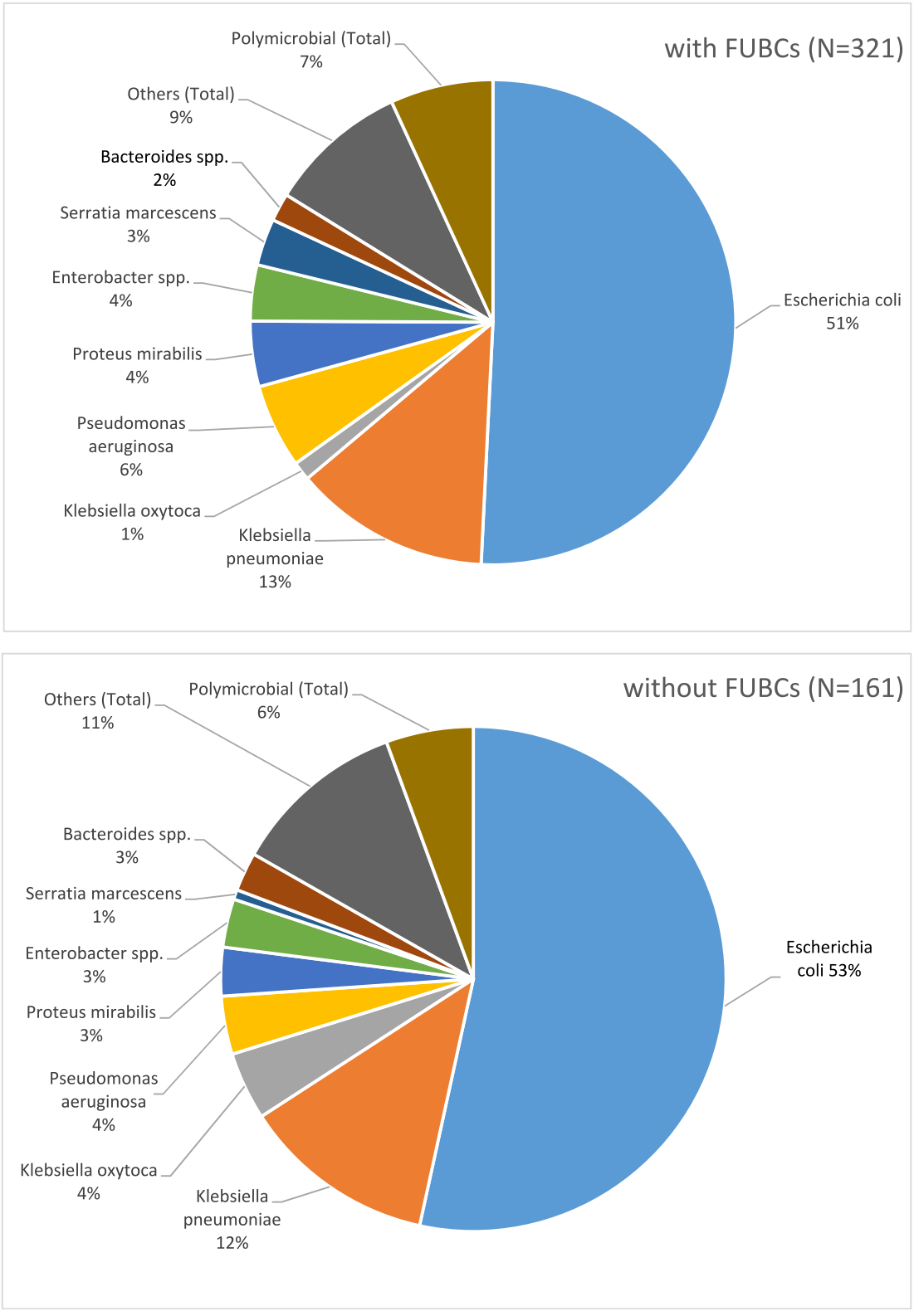

Fig. 2. Microbiology of Index Blood Cultures in Those with and Without FUBCs. Diagrams show distribution of GN pathogens in the two groups. Escherichia coli caused more than half of the cases of index bacteremia in both groups (51% of those with FUBCs and 53% of those without FUBCs) followed by Klebsiella pneumoniae (13% of those with FUBCs and 12% in those without FUBCs). Abbreviations: FUBCs, follow-up blood cultures; GN, Gram-negative.

Table 2. Outcomes.

Variable	with FUBCs (N = 321)	without FUBCs (N = 161)	*P*-value
30-day mortality	9 (2.9%)	4 (2.7%)	>0.999
Re-admission within 30 days	67 (21.4%)	37 (23.4%)	0.704
Length of stay	7 [5, 11]	5 [4, 7]	<0.001
Duration of antibiotic treatment	14 [10, 14]	11 [10, 14]	<0.001
Needed Intensive Care	133 (41.4%)	41 (25.5%)	<0.001

Abbreviations: FUBCs, follow-up blood cultures; N, number.
Note. *P*-values come from Mann–Whitney U and χ^2-tests depending on the distribution of the variable.

Table 3. FUBCs characteristics.

Variable	N = 321
Mean number of FUBCs	1.19 (SD 0.44)
Negative FUBCs	309 (96.3%)
Positive FUBCs	
Same pathogen (persistent bacteremia)	9 (2.8%)
Different pathogen	2 (0.6%)
Contaminant	1 (0.3%)
At time of FUBC	
Fever (>100.3 °F)	47 (14.6%)
Hypotension (SBP < 90, or on vasopressors)	22 (6.9%)
Mean WBC count	12 (SD 6.74)
Recorded reason for obtaining FUBC	91 (28.5%)
To document clearance	69 (75.8%)
Fever	18 (19.8%)
Others (leukocytosis, high lactate, unclear source)	4 (4.4%)

Abbreviations: FUBCs, follow-up blood cultures; N, number; SBP, systolic blood pressure; WBC, white blood cell.
Note. *P*-values come from t-tests, chi-squared tests, and Fisher's exact tests depending on the distribution of the variable.

hospitalization compared to 25.5% in those without FUBCs ($P < 0.001$). It is reasonable to assume that FUBCs were obtained in these patients because they were more critically ill.

We found that 89.1% of those in whom FUBCs were obtained were on effective antibiotic therapy as determined by in vitro susceptibility testing of their index blood cultures. When patients present with suspected infection, they very often receive empiric antibiotic therapy until further evaluation is completed. A study of patients presenting with severe sepsis found a 50% reduction in the sensitivity of blood cultures obtained after initiation of empiric treatment when pre-antimicrobial cultures are positive.[19] C.S. Scheer et al. in their study of patients admitted to the ICU with sepsis and in whom blood cultures were obtained prior to antibiotic initiation, found a 30% loss of pathogen detection in post-antibiotic blood cultures. Furthermore, GN pathogens were less likely to be detected in post-antibiotic cultures.[20] This may explain the very low yield of FUBCs with only 2.8% with persistent bacteremia in our study. A new pathogen was detected in 2 patients (0.6%) in the FUBCs group. Similar to our study, new pathogens were detected in 0.72% of FUBCs in a study of patients during the first 72 h of antibiotic use.[21] It is important however, to be aware of the characteristics of special populations in whom the benefit of FUBCs while on antibiotics cannot be completely dismissed and may be clinically warranted. One such population is patients with high-risk febrile neutropenia where cultures obtained while on antibiotics can be a valuable diagnostic tool with a 7% positivity rate and can lead to change of antibiotic regimen based on the results.[22]

While routine FUBCs were low yield in our study, certain patients in whom they may be indicated require special attention. One study found nosocomial acquisition, polytrauma, neutropenia, hematopoietic stem cell and solid organ transplantation, endovascular foci, and *Pseudomonas aeruginosa* to be independent risk factors for breakthrough bacteremia while on appropriate antibiotics.[23] Breakthrough bacteremia was an independent predictor of mortality further highlighting the importance of establishing this diagnosis, in order to optimize therapy and look for potential sources of infection.[23] Lee et al. identified longer hospital stay before antibiotic administration, hematologic malignancy, persistent neutropenia, immunosuppressant use, and previous colonization by causative microorganisms to be independent risk factors for breakthrough GNB while receiving carbapenem therapy, however, there was a predominance of multidrug resistant and carbapenem resistant organisms in their study.[24] Mitaka et al. aimed to identify patients with risk factors for positive FUBCs in GNB and found ESRD on hemodialysis, presence of intravascular devices, and bacteremia due to multidrug resistant Gram-negative pathogens to be independently associated with positivity.[25] 9.2% of the patients who had FUBCs in their study had the same pathogen isolated as opposed to 2.8% in ours. The yield was 15% for those who had risk factors and only 3.3% for those who had none of the risk factors.[25] It is worth noting that in our study, only 6.5% of patients with FUBCs had ESRD and 5.3% had central intravascular catheters which may explain the difference in yield in our study compared to that of Mitaka et al.

We found a statistically significant difference in the mean duration of antibiotic therapy between the two groups, 14 days in those with FUBCs compared to 11 days in those without ($P < 0.001$). It is not clear if patients in the FUBCs group were perceived to be sicker and as such given longer duration of antibiotics. The duration of antibiotic therapy for GNB is variable with no clear defining guidelines, but recent studies have found no difference in mortality and no higher risk of clinical failure when shorter courses of antibiotics are given compared to longer courses.[26,27] Shorter antibiotic duration exposes patients to less side effects including *Clostridioides difficile* infection.

The hospital LOS was longer in those with FUBCs obtained, 7 days compared to 5 days in those without FUBCs ($P < 0.001$). It is possible that obtaining FUBCs prolongs hospital stay while results are awaited at least in a proportion of the cases. However, we cannot completely rule out the possibility that sicker patients had more frequent blood cultures obtained and were admitted for a longer period of time. A longer hospital stay unnecessarily exposes the patient to the risk of acquiring nosocomial infections and increases healthcare costs. The 30-day readmission rate was not different between the two groups, 21.4% in those with FUBCs, and 23.4% in those without ($P = 0.704$).

We acknowledge that factors such as hospital LOS and antibiotic duration may very well be intertwined, so that longer hospitalization correlated with longer duration of therapy in the same patients. There would likely be an overlap of these with need for ICU stay as well. We did not further analyze these relations in the current study, limiting our scope to the stated primary and secondary objectives. Our institution, however, is currently part of an ongoing larger-scale multi-center study exploring multiple aspects of Gram-negative bacteremia, and we aim to look at these and other factors influencing FUBC in a more thorough manner.

Our study has certain limitations. The retrospective design may have led to selection bias. We had low numbers of patients with nosocomial acquisition, ESRD, intravascular devices, and intra-abdominal source of bacteremia which may have skewed our results towards more negative FUBCs. It is a single center study and it is unclear if results can be applicable to other healthcare settings. Additionally, we may have been unable to capture all reasons for why physicians ordered FUBCs and that were not documented in the medical chart. We however recorded factors that may have influenced the decision to order FUBCs such as fever, hypotension or hemodynamic compromise, the presence of an indwelling intravenous catheter, and nosocomial acquisition, in order to better understand the practice of FUBCs. We were unable to identify predictors of positivity in FUBCs secondary to the small number of positive FUBCs.

5. Conclusion

In conclusion, there was no statistically significant difference in the outcomes of 30-day mortality and 30-day readmission rates between those with or without FUBCs in GNB. FUBCs were associated with longer duration of antibiotic therapy and hospital LOS. Our findings suggest that FUBCs are low yield in GNB and their routine use may not be required in all patients. Prospective studies are needed to further examine the utility of this practice in GNB.

Disclaimer

A poster of this research was presented at IDWeek 2020 (October 2020), Philadelphia, USA, and abstract was published in the journal *Open Forum Infectious Diseases* IDWeek 2020 Abstracts supplement (doi.org/10.1093/ofid/ofaa439.331).

Funding

This work was supported by the Trinity Health St. Joseph Mercy Hospital Ann Arbor Research Department.

Conflict of interest

None of the authors have any conflicts of interest to declare. All authors had access to the data and a role in writing the manuscript.

Acknowledgments

Aditee Dash, MD (Department of Internal Medicine, Trinity Health St. Joseph Mercy Hospital Ann Arbor, MI), assisted with chart review. Jeremy Albright, PhD (Methods Consultants of Ann Arbor, Ypsilanti, MI) performed the statistical analysis for this study. Ali Abunayla, MBChB, coordinated as research project manager (Department of Academic Research, Trinity Health St. Joseph Mercy Hospital Ann Arbor, MI).

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