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Research Paper

Impact of follow up blood cultures on outcomes of patients with community-onset gram-negative bloodstream infection

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ABSTRACT

Background: The role of follow up blood cultures (FUBC) in the management of gram-negative bloodstream infection (GN-BSI) remains controversial. This retrospective cohort study examines the association between obtaining FUBC and mortality in GN-BSI.

Methods: Hospitalized adults with community-onset GN-BSI at Prisma Health-Midlands hospitals in South Carolina, USA from January 1, 2010 to June 30, 2015 were identified. Patients who died or were discharged from hospital within 72 h were excluded to minimize impact of survival and selection biases on results, respectively. Multivariate Cox proportional hazards regression was used to examine association between obtaining FUBC and 28-day all-cause mortality after adjustment for the propensity to obtain FUBC.

Findings: Among 766 patients with GN-BSI, 219 (28.6%) had FUBC obtained and 15 of 219 (6.8%) FUBC were persistently positive. Overall, median age was 67 years, 438 (57%) were women, 457 (60%) had urinary source of infection, and 426 (56%) had BSI due to *Escherichia coli*. Mortality was significantly lower in patients who had FUBC obtained than in those who did not have FUBC (6.3% vs. 11.7%, log-rank $p = 0.03$). Obtaining FUBC was independently associated with reduced mortality (hazards ratio 0.47, 95% confidence intervals: 0.23–0.87; $p = 0.02$) after adjustments for age, chronic comorbidities, acute severity of illness, appropriateness of empirical antimicrobial therapy, and propensity to obtain FUBC.

Interpretation: Improved survival in hospitalized patients with GN-BSI who had FUBC is consistent with the results of recent publications from Italy and North Carolina supporting utilization of FUBC in management of GN-BSI.

Funding: This study had no funding source.

Research in Context

Evidence before this study

Obtaining follow up blood cultures (FUBC) in patients with gram-negative bloodstream infection (GNBSI) is not routinely recommended since prior literature suggests low overall yield of FUBC and high predictability of FUBC results based on initial response to antimicrobial therapy. However, two more recent observational cohorts from tertiary care medical centers have reported an association between obtaining FUBC and lower mortality possibly due to optimization of clinical and antimicrobial management. Recent studies have also identified clinical and microbiological risk factors for persistent GN-BSI, including hemodialysis, central venous catheter source of infection, receipt of inappropriate empiri-

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cal antimicrobial therapy, and GN-BSI due to Serratia species and Pseudomonas aeruginosa.

Added value of this study

The current study confirms the association between obtaining FUBC and lower mortality in a GN-BSI cohort with relatively low prevalence of major chronic medical conditions, P. aeruginosa bloodstream infections, and receipt of inappropriate empirical antimicrobial therapy at two community hospitals. Obtaining FUBC appears to provide additional opportunities for source control. The probability of persistent GN-BSI is high in the presence of either clinical or microbiological risk factors but is not entirely negligible in the absence of these variables.

Implications of all the available evidence

Based on the results of the current and recent studies, obtaining FUBC appears to have a role in the management of more patients with GN-BSI than previously suggested by previous literature. Stratification of patients based on clinical and microbiological risk factors for persistent GN-BSI remains valuable to minimize routinely obtaining FUBC in low risk patients.

1. Introduction

Bloodstream infection (BSI) is the seventh leading cause of death in the United States [1]. Appropriate clinical and antimicrobial management of BSI are crucial to improve patient survival [2,3]. The importance of follow up blood cultures (FUBC) has been well established in *Staphylococcus aureus* BSI where obtaining FUBC has been associated with improved clinical outcomes [4,5]. However, the role of FUBC in the management of gram-negative BSI (GN-BSI) remains controversial. Prior studies suggested low yield of FUBC in most patients with GN-BSI [6–9], whereas two more recent investigations demonstrated potential benefit from FUBC [10,11]. In an observational cohort study of GN-BSI in Italy, Giannella and colleagues reported significantly lower mortality in patients with GN-BSI who had FUBC obtained than those who did not have FUBC [10]. Maskarinec and colleagues demonstrated similar results in a large multicenter cohort in North Carolina [11]. This retrospective, observational cohort study examined the association between obtaining FUBC and 28-day all-cause mortality in patients with community-onset GN-BSI.

2. Methods

2.1. Settings

The study was conducted at Prisma Health Richland and Baptist Hospitals in Columbia, South Carolina, USA. The two community-teaching hospitals combine for over 1000 licensed beds and provide medical, surgical, and subspecialty care for the residents of Richland and surrounding counties in the Midlands region of South Carolina. The Institutional Review Board at Prisma Health-Midlands approved the study and waived informed consent on April 8, 2020 (Amendment 7 for study #Pro00034526).

The Prisma Health-Midlands antimicrobial stewardship and support team receives real-time alerts for positive blood cultures and provides recommendations to primary healthcare providers to optimize source control and antimicrobial management based on local institutional guidelines [12,13]. These management guidelines do not recommend for or against obtaining FUBC in patients with GN-BSI [13]. The decision to obtain FUBC was solely made by the primary healthcare provider caring for the patient.

2.2. Case ascertainment

Patients ≥18 years old with first episodes of monomicrobial BSI due to gram-negative bacilli hospitalized at Prisma Health-Midlands hospitals from January 1, 2010 to June 30, 2015 were identified through microbiology laboratory databases (n = 1376). Patients with polymicrobial (n = 166) and recurrent episodes of BSI (n = 47) were excluded. Nosocomial GN-BSI (n = 238) were excluded to reduce the potential impact of primary admission diagnoses on outcomes. Patients who died within 72 h of collection of index blood culture (n = 74) were excluded to minimize the impact of survival bias on the analysis. In addition, patients who were discharged within 72 hours of hospital admission (n = 84) were excluded to reduce the effect of selection bias based on initial response to antimicrobial therapy on the results. One patient was excluded due to missing baseline acute severity of illness variables. Overall, 766 hospitalized adults with community-onset GN-BSI were enrolled in the study.

2.3. Definitions

FUBC were defined as repeat blood cultures obtained between 24 and 96 h from initial positive blood culture for gram-negative bacilli. The source of GN-BSI was defined based on the Centers for Disease Control and Prevention criteria [14]. The Pitt bacteremia score was used to measure acute severity of illness at onset of GN-BSI, and the Charlson comorbidity index score was used to summarize chronic comorbidities (Supplementary Appendix 1) [15,16]. Appropriateness of empirical antimicrobial therapy was defined based on in vitro antimicrobial susceptibility testing results, dose, and route of empirical antimicrobial regimen [17]. Briefly, empirical antimicrobial therapy was considered inappropriate if the bloodstream isolate was non-susceptible to all antimicrobials used in the first 48 hours after collection of index blood culture, patients received antimicrobial doses lower than the recommended in the package insert for creatinine clearance at the time, or if patients received empirical oral antimicrobials other than fluoroquinolones [17]. Antimicrobial susceptibility testing was performed and interpreted according to Clinical Laboratory and Standards Institute criteria. Delayed clinical response to initial antimicrobial therapy was defined as presence of ≥2 early clinical failure criteria between 72 and 96 h of index GN-BSI (Supplementary Appendix 1) [18]. Patients with GN-BSI evaluable for source control included those with intra-abdominal, skin and soft tissue, and central venous catheter infections since imaging is not routinely recommended and opportunities for source control are scarce among those with other sources of infection. Mean time to source control among patients with evaluable sources was defined as time from obtaining initial blood culture to definitive source control procedure (e.g. abscess drainage, removal of central venous catheter, etc.). Persistent GN-BSI was defined as growth of the same genus and species of gram-negative bacillus in FUBC as in the initial blood culture.

2.4. Statistical analysis

The primary objective of this retrospective observational cohort study was to examine the association between obtaining FUBC and 28-day all-cause mortality in hospitalized patients with GN-BSI. Since obtaining FUBC was not randomized, propensity score analysis was used to adjust for the propensity for obtaining FUBC. Multivariate logistic regression analysis was performed to identify baseline clinical characteristics associated with obtaining FUBC in patients with GN-BSI. Variables associated with obtaining FUBC in

the univariate analysis with $p < 0.05$ were included in the multivariate logistic regression model using backward selection criteria. The propensity for obtaining FUBC was calculated based on the predictors of obtaining FUBC in the multivariate logistic regression model.

Kaplan Meier analysis was used to examine 28-day mortality in patients who did or did not have FUBC obtained. Patients were followed for 28 days from onset of GN-BSI or until death. Patients lost to follow up within 28 days were censored on the date of last healthcare visit. Cox proportional hazards regression model was used to examine association between obtaining FUBC and 28-day all-cause mortality after adjusting for the propensity of obtaining FUBC. Univariate Cox model was used to examine risk factors for 28-day mortality. Variables associated with mortality in univariate analysis ($p < 0.05$) were included in the multivariate Cox model. The logit-transformed probability of obtaining FUBC was also included in the multivariate Cox model to adjust for the propensity of obtaining FUBC. Variables associated with both the propensity to obtain FUBC and mortality were accounted for once in the multivariate Cox model. Testing for co-linearity was performed and variance inflation factor for correlation between any two independent predictors was <4. To confirm the results, an alternate multivariate Cox proportional hazards regression model was designed by including the individual variables of the propensity score in the model rather than the propensity score.

Secondary outcomes examined mortality based on FUBC results and mean time to source control in patients with and without FUBC. Kaplan-Meier analysis was used to compare 28-day mortality between patients with persistent GN-BSI and those with negative FUBC. Student's t-test was used to examine mean time to source control in patients with and without FUBC among those with evaluable sources of GN-BSI.

JMP Pro version 13.0 (Cary, North Carolina, USA) was used for statistical analysis. Statistical significance was based on two-sided p-value <0.05.

2.5. Role of the funding source

The study had no source of funding. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

3. Results

3.1. Baseline clinical characteristics

During the 66-month study period, 766 hospitalized patients with community-onset GN-BSI met study inclusion and exclusion criteria and were included in the analysis. Overall, the median age was 67 years (interquartile range 55-79 years) and 438 (57%) were women. The study population was diverse with 369 (48%) Caucasians, 373 (49%) African Americans, and 24 (3%) other races/ethnicities. The urinary tract was the most common source of GN-BSI (457; 60%), followed by intra-abdominal infections (89; 12%), central venous catheter infections (63; 8%), skin and soft tissue infections (34; 4%), respiratory tract infections (29; 4%), other (11; 1.4%), and unknown source of infection (83; 11%). *Escherichia coli* was the most common bloodstream isolate (426; 56%), followed by *Klebsiella* species (133; 17%), *Proteus mirabilis* (58; 8%), *Enterobacter* species (37; 5%), *Pseudomonas aeruginosa* (36; 5%), *Serratia* species (16; 2%) and other gram-negative bacilli (60; 8%).

FUBC were obtained in 219 (28.6%) patients with GN-BSI. Compared to patients who did not have FUBC obtained, those with FUBC were relatively younger, less likely to have indwelling urinary catheter and *E. coli* BSI, and more likely to have end-stage renal disease and indwelling central venous catheters. The median Pitt bacteremia score was numerically lower in patients with FUBC obtained than those without FUBC, but the small difference was not statistically significant (Table 1). After adjustments in the multivariate logistic regression model, end-stage renal disease (OR 6.10, 95% CI: 0.38–10.99; $p < 0.001$) and presence of indwelling central venous catheters (OR 1.62, 95% CI: 1.02–2.65; $p = 0.045$) were independently associated with obtaining FUBC and were included in the score modelling the propensity to obtain FUBC.

3.2. Association between obtaining FUBC and mortality

During 28 days of follow up, a total of 69 patients died (12 in the FUBC group and 57 in patients without FUBC). Mortality was significantly lower in patients who had FUBC obtained than in those who did not have FUBC (6.3% vs. 11.7%, log-rank $p = 0.03$; Fig. 1). Univariate Cox proportional hazards model results for risk factors of 28-day mortality are demonstrated in Table 2. After adjustments for the propensity to obtain FUBC and other potential confounders in the multivariate Cox model, obtaining FUBC was independently associated with reduced mortality in patients with GN-BSI (HR 0.47, 95% CI: 0.23–0.87; $p = 0.02$; Table 3). An alternate model adjusting for the individual components of the propensity score yielded similar results (Supplementary Table 1)

3.3. Secondary outcomes

In 219 patients who had FUBC, 15 (7%) had persistent positive FUBC. The median age of patients with persistent GN-BSI was 60 years and 8 (53%) were women. Notably, 9 (60%) patients with persistent GN-BSI had end-stage renal disease, 3 (20%) had BSI due to *Serratia* species, and 5 (33%) had delayed clinical response to initial antimicrobial therapy. The proportion of patients with persistent GN-BSI by major clinical and microbiological risk factors are demonstrated in Table 4. The 28-day mortality was 13.9% in patients with persistent GN-BSI compared to 5.7% in those with negative FUBC (log-rank $p = 0.23$).

There were 83 and 103 patients with evaluable sources of GN-BSI among those with and without FUBC, respectively. The mean time to source control was significantly longer in patients who had FUBC obtained compared to those who did not have FUBC (3.8 vs. 2.1 days, respectively, $p = 0.02$).

4. Discussion

The current study results confirm recent findings from large cohorts of patients with GN-BSI in Italy and North Carolina [10,11]. Obtaining FUBC was significantly associated with nearly 50% decline in 28-day mortality after adjustments for the propensity to obtain FUBC and other risk factors for mortality.

This consistent decline in mortality in association with obtaining FUBC was remarkable given the vast differences in patient populations, microbiology, and clinical practice among the three cohorts that combined over 4000 patients [10,11]. Inclusion of patients from tertiary care referral centers in the two earlier studies as compared to community hospitals in the current investigation resulted in more complex patient populations with higher proportion of cancer and other comorbidities [10,11]. Whereas nearly one-half and one-third of GN-BSI were hospital-acquired in the studies from Italy and North Carolina, respectively [10,11], the current cohort included only patients with community-onset GN-BSI. This led to considerably higher proportion of BSI due to *P. aeruginosa* and other non-fermenting gram-negative bacilli in the first two cohorts than the current study [10,11]. Differences in the source of GN-BSI were also noted with predominance of the urinary tract (60%) in the current cohort compared to the other two studies (32–38%) [10,11]. Various study settings and geographical

Table 1
Baseline clinical characteristics of patients with and without follow up blood cultures.

Variable	FUBC (n = 219)	No FUBC (n = 547)	Odds ratio (95% CI)	p
Age, median (IQR)	65 (52–75)	68 (56–79)	0.89[a] (0.81–0.97)	0.01
Female sex	123 (56)	315 (58)	0.94 (0.69–1.29)	0.72
Caucasian race	99 (45)	270 (49)	0.85 (0.62–1.16)	0.30
Diabetes mellitus	91 (42)	232 (42)	0.97 (0.70–1.33)	0.83
End-stage renal disease	55 (25)	22 (4)	8.00 (4.74–13.52)	<0.001
Liver cirrhosis	7 (3)	22 (4)	0.79 (0.33–1.87)	0.59
Cancer	39 (18)	81 (15)	1.25 (0.82–1.90)	0.30
Immune compromised host	32 (15)	60 (11)	1.39 (0.88–2.20)	0.16
Charlson comorbidity index score, median (IQR)	2 (1-3)	2 (1-3)	1.04[b] (0.97–1.13)	0.26
Indwelling urinary catheter	11 (5)	54 (10)	0.48 (0.25–0.94)	0.03
Indwelling CVC	60 (27)	56 (10)	3.31 (2.21–4.96)	<0.001
Low inoculum source of BSI[c]	142 (65)	378 (69)	0.82 (0.59–1.15)	0.25
Bloodstream isolate				
Escherichia coli	98 (45)	328 (60)	0.54 (0.39–0.74)[d]	<0.001
Klebsiella species	42 (19)	91 (17)		
Proteus mirabilis	18 (8)	40 (7)		
Enterobacter cloacae	15 (7)	22 (4)		
Pseudomonas aeruginosa	10 (5)	26 (5)		
Serratia species	11 (5)	5 (1)		
Other	25 (11)	35 (6)		
Pitt bacteremia score, median (IQR)	1 (1-3)	2 (1-3)	0.94[b] (0.86–1.02)	0.12
Inappropriate empirical antimicrobial therapy	15 (7)	41 (7)	0.91 (0.49–1.68)	0.76
Delayed clinical response to initial therapy[e]	72 (33)	197 (36)	0.87 (0.62–1.21)	0.41

Data are demonstrated as number (percentage) unless otherwise specified.
FUBC: follow up blood cultures; CI: confidence intervals; IQR: interquartile range; CVC: central venous catheter; BSI: bloodstream infection.
[a] Odds ratio per decade of age.
[b] Odds ratio per point.
[c] Bloodstream infection secondary to urinary or central venous catheter infection.
[d] Odds ratio for *E. coli* vs. other bloodstream isolates.
[e] ≥2 early clinical failure criteria between 72 and 96 h of bloodstream infection [18].

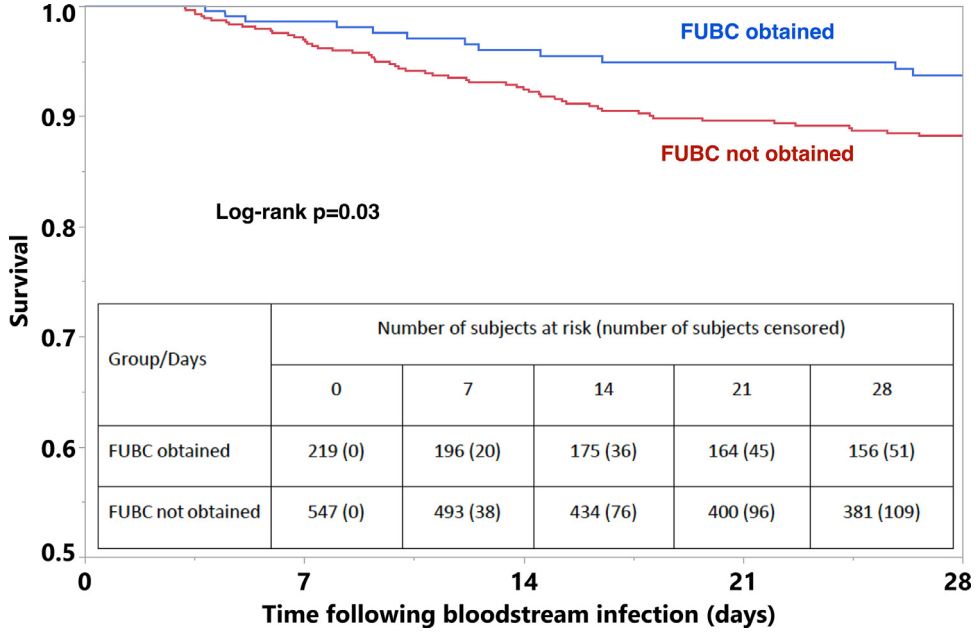

Fig. 1. Kaplan–Meier survival curves of patients with and without follow up blood cultures (FUBC).

locations likely influenced antimicrobial resistance and empirical antimicrobial therapy. The proportion of patients receiving appropriate empirical antimicrobial therapy was 68%, 84%, and 93% in Italy, North Carolina, and South Carolina, respectively [10,11]. The medical practice also varied between the three sites; 68% of patients with GN-BSI in North Carolina had FUBC obtained as compared to only 29% in South Carolina and 18% in Italy [10,11]. These differences likely contributed to the lower overall proportion of persistently positive FUBC in the current study (7%) compared to the previous two cohorts (20–38%) [10,11].

Obtaining FUBC is considered the standard of care in patients with *S. aureus* BSI [4,5]. Identifying patients with persistent *S. aureus* BSI allows expanding diagnostic work up to identify complications and optimize source control and antimicrobial management. This likely explains the association between obtaining FUBC and improved survival in patients with *S. aureus* BSI [4]. Moreover, patients with persistent *S. aureus* BSI have higher mortality than those with negative FUBC [19,20]. Similar findings have been demonstrated in recent cohorts of GN-BSI, including the current study [10,11]. Obtaining FUBC was associated with reduced mortal-

Table 2
Univariate Cox proportional hazards regression model for 28-day mortality.

Risk factor	Hazards ratio (95% CI)	p
Age (per decade)	1.20 (1.03–1.41)	0.02
Female sex	0.75 (0.47–1.20)	0.23
Caucasian race	1.59 (1.00–2.60)	0.05
Diabetes mellitus	0.75 (0.45–1.22)	0.25
End-stage renal disease	0.51 (0.15–1.23)	0.15
Liver cirrhosis	1.08 (0.26–2.89)	0.90
Cancer	4.27 (2.64–6.86)	<0.001
Immune compromised host	2.60 (1.48–4.36)	0.001
Charlson comorbidity index score (per point)	1.23 (1.13–1.33)	<0.001
Indwelling urinary catheter	0.82 (0.29–1.84)	0.66
Indwelling CVC	1.02 (0.51–1.87)	0.94
Low inoculum source of BSI[a]	0.53 (0.33–0.86)	0.01
E. coli BSI	0.60 (0.37–0.97)	0.04
Pitt bacteremia score (per point)	1.29 (1.21–1.40)	<0.001
Inappropriate empiric therapy	2.44 (1.21–4.46)	0.001
FUBC	0.52 (0.26–0.93)	0.03

CI: confidence intervals; CVC: central venous catheter; BSI: bloodstream infection; FUBC: follow up blood cultures.
[a] Bloodstream infection secondary to urinary or central venous catheter infection.

Table 3
Multivariate Cox proportional hazards regression model results for 28-day mortality.

Risk factor	Hazards ratio (95% CI)	p
Age (per decade)	1.34 (1.12–1.61)	0.001
Cancer	3.52 (1.82–6.73)	<0.001
Immune compromised host	1.49 (0.77–2.81)	0.23
Charlson comorbidity index score (per point)	1.11 (0.99–1.24)	0.07
Low inoculum source of BSI[a]	0.73 (0.45–1.21)	0.22
E. coli BSI	0.81 (0.48–1.36)	0.43
Pitt bacteremia score (per point)	1.37 (1.25–1.49)	<0.001
Inappropriate empirical therapy	2.20 (1.08–4.11)	0.03
Propensity to obtain FUBC	0.62 (0.15–1.87)	0.43
FUBC	0.47 (0.23–0.87)	0.02

CI: confidence intervals; BSI: bloodstream infection; FUBC: follow up blood cultures.
[a] Bloodstream infection secondary to urinary or central venous catheter infection.

Table 4
Proportion of patients with persistent gram-negative bloodstream infection based on clinical and microbiological risk factors.

Microbiological/Clinical risk factors	ESRD[a]	CVC source[a]	Inappropriate empirical therapy[a]	None	Total
Serratia* species or *P. aeruginosa	4/8 (50%)	4/12 (30%)	1/3 (33%)	0/9 (0%)	4/21 (19%)
Other bloodstream isolates	5/47 (11%)	3/31 (10%)	1/12 (8%)	5/138 (4%)	11/198 (6%)
Overall	9/55 (16%)	7/43 (16%)	2/15 (13%)	5/147 (4%)	15/219 (7%)

ESRD: end-stage renal disease; CVC: central venous catheter.
[a] Risk factors are not exclusive as one patient may have multiple risk factors. Risk factors for persistent gram-negative bloodstream infection are derived from the previous literature [11,21–23].

ity in patients with GN-BSI [10,11]. The current study results suggest that obtaining FUBC allowed further opportunities for source control given mean time to source control >3 days in patients with GN-BSI who had FUBC obtained. Recent investigations from Italy and North Carolina also presented valid arguments supporting the role of FUBC in optimizing source control and antimicrobial management [10,11]. In addition, persistent GN-BSI was significantly associated with higher mortality than negative FUBC in the North Carolina cohort [11]. The current study demonstrated numerically higher mortality in patients with persistent GN-BSI than those with negative FUBC. The difference was not statistically significant due to the relatively small number of patients who had FUBC obtained and low proportion with persistently positive FUBC.

Higher mortality in patients without FUBC implies missed opportunities for source control, identification of complications, and optimization of antimicrobial management in this group compared to patients who had FUBC obtained. For example, in a patient who already underwent drainage of an intra-abdominal abscess, the finding of persistent GN-BSI may lead to placement of an additional drain or manipulation of the existing one to optimize source control. Similarly, persistent GN-BSI in a woman with back pain due to first episode of acute pyelonephritis may lead to renal imaging to identify an obstructing ureteric stone or lumbar imaging to identify a complication such as discitis or vertebral osteomyelitis. A doppler ultrasound examination in a patient with an indwelling central venous catheter for hemodialysis and persistent GN-BSI may reveal the diagnosis of septic deep venous thrombosis and allow optimization of antimicrobial treatment duration. While the proportion of patients with persistently positive FUBC varies between studies based on complexity of patient populations and frequency of obtaining FUBC in clinical practice, this proportion cannot be extrapolated to patients without FUBC in an observational cohort design that does not entail randomization. A clinical trial randomizing one group of patients with GN-BSI to have FUBC, as opposed to a comparator group where obtaining FUBC is left to the discretion of the treating clinician, is better equipped to answer this question. In the meantime, FUBC appear to have a role in the management of patients with GN-BSI who are expected to remain hospitalized for >72 h [10,11].

Identification of patients at high risk of persistent GN-BSI is valuable to optimize the use of laboratory resources and reduce the number of low-yield FUBC. Maskarinec and colleagues developed a scoring system to predict probability of persistent GN-BSI [11]. Hemodialysis, corticosteroid use, cardiac devices, source of infection other than urinary or gastrointestinal tracts, time to appropriate antimicrobial therapy >24 h, and *Serratia* species were risk factors for persistent GN-BSI. However, the risk of persistent GN-BSI was 9% even in the absence of all risk factors [11]. Another recent study from South Korea identified hemodialysis, BSI secondary to central venous catheter infection, non-eradicable source of infection, and unfavorable clinical response to therapy as predictors of persistent GN-BSI [21]. The current cohort does not have adequate power to formally validate either model. End-stage renal disease requiring hemodialysis and BSI due to *Serratia* species were more common in patients with persistent GN-BSI than in the overall cohort, which is consistent with the two previous studies [11,21]. However, in patients who remained hospitalized for >72 h, initial response to antimicrobial therapy was comparable between patients with persistent GN-BSI and overall cohort. This supports the previous findings of Ceccarelli and colleagues who demonstrated that persistent GN-BSI due to septic thrombophlebitis occurred despite initial clinical improvement on antimicrobial therapy [22].

More recently, Cogliati Dezza and colleagues elegantly summarized and reappraised the evidence in the literature for obtaining FUBC in patients with GN-BSI [23]. Graded recommendations to obtain FUBC were proposed based on clinical and microbiological risk factors derived from prior studies [23]. Despite the small number of patients with persistent GN-BSI in the current cohort, the results seem to be in agreement for the most part with the proposed guidelines in the review [23]. The proportion of patients with persistently positive FUBC ranged from 13% to 19% in the presence of either clinical or microbiological risk factors and exceeded 30% in the presence of both (Table 4). However, 4% of patients with FUBC still had persistently positive FUBC even in the absence of major clinical and microbiological risk factors.

In the current cohort, the decision to obtain FUBC in patients with GN-BSI was left to the primary healthcare provider. The local institutional guidelines for management of GN-BSI did not recommend for or against obtaining FUBC due to the equivocal evidence in the literature at the time [13]. Primary healthcare providers were more likely to obtain FUBC in patients who would likely require placement of a new central venous catheter after bloodstream clearance. This included patients with end-stage renal disease on hemodialysis and those with indwelling central venous catheters prior to GN-BSI. These two variables were included in the propensity model for obtaining FUBC and were accounted for in the multivariate Cox proportional hazards regression model. Adjustment for these two variables individually in the multivariate Cox model also yielded similar results.

Application of strict exclusion criteria upfront to minimize the impact of survival and selection biases on results represents the major strengths in the current work. The inclusion of patients with GN-BSI from community hospitals improves generalizability of the results of previous studies from tertiary care medical centers [10,11]. Propensity score analysis allowed adjustment for potential variables that influenced the decision to obtain FUBC without crowding the final Cox model. The study shares common limitations of observational cohorts, including inability to adjust for unknown or unmeasured confounders. This is particulatly relevant when examining adequacy of source control in the absence of standardized imaging protocols or other measures to identify potential complications from GN-BSI. Examination of risk factors for persistent GN-BSI was not possible due to small number of patients with positive FUBC. Finally, the study was performed at two hospitals located in one city and within the same healthcare system. The local clinical practice of healthcare providers in this area may influence the yield of FUBC and other study results.

In summary, the current study results confirm the findings of two recent large observational cohorts from Italy and North Carolina supporting the role of FUBC in the management of GN-BSI. In patietns with community-onset GN-BSI who are expected to remain hospitalized for >72 hours, obtaining FUBC should be considered, particularly in the context of end-stage renal disease, central venous catheter source of infection, receipt of inappropriate empirical antimicrobial therapy, and BSI due to *Serratia* species among other risk factors for persistent GN-BSI.

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Data sharing statement

Deidentified data in this manuscript will be available upon request from the corresponding author after signing a data sharing agreement.

Contributors

Conceptualization, MNA; methodology, RA, HRW, JJ, PBP, JK and MNA; software, JK and MNA; validation, HRW and MNA; formal analysis, MNA; investigation, RA, HRW, JJ, PBP, JK, and MNA; resources, HRW, JJ, and MNA; data curation, HRW and MNA; writing—original draft preparation, RA; writing—review and editing, HRW, JJ, PBP, JK, and MNA; visualization, RA, HRW, JJ, PBP, and MNA; supervision, JJ and MNA; project administration, HRW, JJ, PBP, JK and MNA; funding acquisition, none. All authors have read and agreed with the contents of this manuscript.

Declaration of Competing Interest

RA, JK, and MNA: no conflicts

HRW: bioMérieux, Speaker's Bureau (outside the submitted work); JJ: bioMérieux, Speaker's Bureau, Merck, Advisory Board (outside the submitted work); PBB: bioMérieux, Speaker's Bureau, Kedrion Biopharma, Advisory Board, research grant (outside the submitted work).

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eclinm.2021.100811.

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