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Empirical Fluoroquinolones Versus Broad-Spectrum Beta-Lactams for Gram-Negative Bloodstream Infections in the Absence of Antimicrobial Resistance Risk Factors

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Empirical fluoroquinolones versus broad-spectrum beta-lactams for Gram-negative bloodstream infections in the absence of antimicrobial resistance risk factors

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ABSTRACT

Objectives: Increasing antimicrobial resistance rates limit empirical antimicrobial treatment options for Gram-negative bloodstream infections (GN-BSI). However, antimicrobial resistance may be predicted based on patient-specific risk factors using precision medicine concepts. This retrospective, 1:2 matched cohort examined clinical outcomes in hospitalized adults without major risk factors for antimicrobial resistance receiving empirical fluoroquinolones or broad-spectrum beta-lactams (BSBL) for GN-BSI at Prisma Health-Midlands hospitals in Columbia, SC, USA from January 2010 through June 2015.

Methods: Multivariable logistic regression was used to examine early treatment failure at 72–96 h from GN-BSI. Cox proportional hazards regression was used to examine 28-day mortality and hospital length of stay (HLOS).

Results: Among 74 and 148 patients receiving empirical fluoroquinolones and BSBL for GN-BSI, respectively, median age was 68 years, 159 (72%) were women, and 152 (68%) had a urinary source of infection. Early treatment failure rates were comparable in fluoroquinolone and BSBL groups (27% vs. 30%, respectively, odds ratio 0.82, 95% confidence intervals [CI] 0.43–1.54, $P = 0.53$), as well as 28-day mortality (8.9% vs. 9.7%, respectively, hazards ratio [HR] 0.74, 95% CI 0.26–1.90, $P = 0.54$). Median HLOS was 6.1 days in the fluoroquinolone group and 7.1 days in the BSBL group (HR 0.73, 95% CI 0.54–0.99, $P = 0.04$). Transition from intravenous to oral therapy occurred sooner in the fluoroquinolone group than in the BSBL group (3.0 vs. 4.9 days, $P < 0.001$).

Conclusions: In the absence of antimicrobial resistance risk factors, fluoroquinolones provide an additional empirical treatment option to BSBL for GN-BSI. Shorter HLOS in the fluoroquinolone group may be due to earlier transition from intravenous to oral antimicrobial therapy.

1. Introduction

Increasing rates of antimicrobial resistance in both community and healthcare settings limit the utility of fluoroquinolones for empirical therapy of hospitalized patients with Gram-negative bloodstream infections (GN-BSI) [1–3]. This leaves many patients with serious penicillin and cephalosporin allergies without safe and effective antimicrobial agents for empirical therapy [4]. In addition, it also limits early oral antimicrobial switch options in patients who demonstrate rapid clinical improvement soon after hospital admission. Recent studies have demonstrated the feasibility of an intravenous to oral antimicrobial switch strategy in GN-BSI after 3 days, when conventional in vitro antimicrobial susceptibility testing results became available [5–8]. However, in the era of precision medicine, antimicrobial resistance may be estimated using clinical risk prediction tools based on patient-specific risk factors for antimicrobial resistance [9–12]. More specifically, recent literature has demonstrated <10% resistance rates to both fluoroquinolones and third-generation cephalosporins in bloodstream isolates of patients without major risk factors for antimicrobial resistance, such as recent antimicrobial use,

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ambulatory gastrointestinal or genitourinary procedures, or residence in skilled nursing facilities [11,12].

In this study, it was hypothesized that hospitalized patients without major risk factors for antimicrobial resistance treated empirically with fluoroquinolones for GN-BSI had comparable clinical outcomes to those receiving broad-spectrum beta-lactams (BSBL). The primary aim of this matched retrospective cohort study was examination of early treatment failure between 72 and 96 h of GN-BSI based on empirical antimicrobial therapy. Secondary outcomes included 28-day mortality and hospital length of stay (HLOS).

2. Materials and methods

2.1. Settings

The study was conducted at Prisma Health-Midlands (previously Palmetto Health) Richland and Baptist Hospitals in Columbia, South Carolina, USA. These are the two largest hospitals within Prisma Health-Midlands network in South Carolina. The local Institutional Review Board approved the study and waived informed consent.

2.2. Definitions

Blood cultures were processed using standard microbiology techniques according to the Clinical and Laboratory Standards Institute (CLSI). In vitro antimicrobial susceptibility testing was performed via the VITEK® 2 system (bioMérieux; Marcy l'Etoile, France) throughout the study period. The site of infection acquisition and primary source of GN-BSI were classified as previously defined [13,14]. HLOS was defined as time from collection of index blood culture to discharge from the hospital. Empirical fluoroquinolone therapy was defined as receipt of intravenous or oral fluoroquinolones within 24 h of collection of index blood cultures and continued for at least 48 h. Empirical BSBL therapy was defined as receipt of intravenous piperacillin/tazobactam, third- or fourth-generation cephalosporins, carbapenems, or aztreonam, within 24 h of GN-BSI and continued for at least 48 h. Appropriateness of empirical antimicrobial therapy was defined based on in vitro antimicrobial susceptibility testing results, route, and dose of empirical antimicrobial regimen as previously defined [15]. Early treatment failure was defined as death within 72 h of GN-BSI or presence of $\geq$2 early clinical failure criteria (ECFC) between 72 and 96 h of GN-BSI [16]. ECFC were recently proposed as objective criteria to determine response to empirical antimicrobial therapy based on variables that independently predicted 28-day mortality or prolonged hospitalization for >14 days. These criteria were assessed between 72 and 96 h of GN-BSI and included: systolic blood pressure <100 mmHg or vasopressor use, heart rate >100 beats/min, respiratory rate $\geq$22 breaths/min or mechanical ventilation, altered mental status, and peripheral white blood cell count >12 000/mm^3 [16]. Sepsis was defined as quick sequential organ failure assessment (qSOFA) score $\geq$2 as per sepsis-3 criteria [17]. All study definitions, variables, and outcomes were determined a priori.

2.3. Case ascertainment

In this quasi-experimental cohort study, all adult patients with monomicrobial BSI due to aerobic Gram-negative bacilli from 1 January 2010 to 30 June 2015 were identified through central microbiology laboratory databases at Prisma Health-Midlands (n = 1163) as previously described [18]. Patients who had at least one major risk factor for antimicrobial resistance, such as recent antimicrobial use, ambulatory gastrointestinal or genitourinary procedures, or residence in skilled nursing facilities (n = 489), were excluded from the study [11,12]. Among 674 patients without major risk factors for antimicrobial resistance, 74 received empirical fluoroquinolone monotherapy, 412 received BSBL monotherapy, and the remaining 188 were empirically treated with either combination or other antimicrobial regimens (Fig. 1). Since treatment allocation was not randomized in this retrospective cohort design, patients receiving fluoroquinolone empirical therapy were randomly matched to those receiving BSBL in a 1:2 fashion based on age (±10 years), sex, and exact bloodstream infection mortality risk score (BSIMRS). The BSIMRS has been derived and validated to predict mortality in patients with GN-BSI and encompasses major comorbidities, source of infection, and acute severity of illness as per the Pitt bacteremia score [19,20]. The Pitt bacteremia score was used as a primary measure of acute severity of illness since it does not include arterial blood gases and other laboratory variables that may not be obtained in all patients, particularly those admitted to the general hospital floors [21]. The modified sequential organ failure assessment (mSOFA) was used as a secondary score of acute severity of illness for reassurance [22]. To avoid enrolling the same patient more than once into the cohort, patients were removed from the screening pool upon study enrolment.

2.4. Statistical analysis

The primary objective of the study was to evaluate impact of empirical antimicrobial therapy on early treatment failure at 72–96 h of GN-BSI. Secondary objectives were 28-day mortality and HLOS in patients who received empirical fluoroquinolones and BSBL.

Since patients in both treatment groups were matched by age, sex, and BSIMRS, the propensity of receiving empirical fluoroquinolones was determined based on differences in non-matched variables. In the multivariable logistic regression modelling the propensity of receiving empirical fluoroquinolones, variables were included if P-value was <0.10 in the univariable model using backward selection. Multivariable logistic regression was then used to examine early treatment failure at 72–96 h of onset of GN-BSI after adjustment for the propensity of receiving empirical fluoroquinolones. Odds ratios (OR) and 95% confidence intervals (CI) were reported to describe the strength of association between each variable and early treatment failure.

Kaplan–Meier analysis was used to examine 28-day mortality in patients receiving empirical fluoroquinolones and BSBL. Patients were followed from time of index blood culture collection for 28 days or until death. This allowed censoring of patients who were lost to follow-up before 28 days from GN-BSI. Patients lost to follow-up were censored at the date of last documented healthcare visit. Log-rank P-value was used to assess the statistical significance of the difference in 28-day mortality between the two treatment groups. Multivariable Cox proportional hazards regression model was used to compare 28-day mortality between fluoroquinolone and BSBL groups after adjustment for the propensity of receiving empirical fluoroquinolones. The proportional hazards assumption was evaluated by plotting the log integrated hazard vs. time from the Kaplan–Meier method. Hazard ratios (HR) with 95% CI were reported to indicate the strength of association between the treatment group and 28-day mortality.

Kaplan–Meier analysis and multivariable Cox proportional hazards regression were also used to examine HLOS following GN-BSI after adjustment for the propensity of receiving empirical fluoroquinolones. Patients were followed from time of collection of index blood culture until discharge from the hospital. Patients who died prior to hospital discharge were censored on the date of death to avoid accounting for early mortality as a favourable outcome. Log-rank P-value was used to assess the statistical significance of

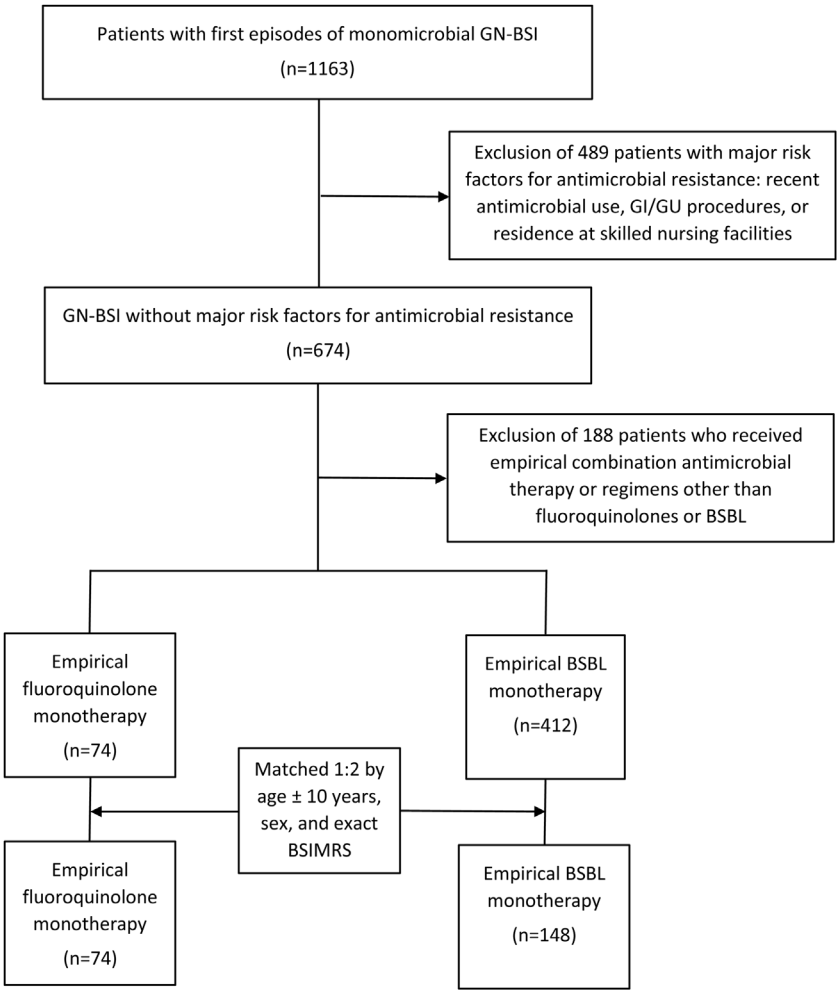

Fig. 1. Flowchart of case ascertainment in study. BSBL, broad-spectrum beta-lactams; BSIMRS, bloodstream infection mortality risk score; GI, gastrointestinal; GN-BSI, Gram-negative bloodstream infection; GU, genitourinary.

the difference in HLOS between patients who received empirical fluoroquinolones and BSBL therapy. HR with 95% CI were presented to demonstrate the strength of association between the treatment group and HLOS.

JMP Pro (version 13.0, SAS Institute Inc., Cary, NC) was used for statistical analysis. The level of significance for statistical testing was defined as $P < 0.05$ (two-sided) unless otherwise specified.

3. Results

3.1. Clinical characteristics of the cohort

Among patients without major risk factors for antimicrobial resistance during the study period, 74 receiving empirical fluoroquinolone monotherapy were matched to 148 who received BSBL for GN-BSI. Since patients were matched by age, sex, and BSIMRS, there were no major differences in baseline demographics or clinical characteristics between the two groups (Table 1). Acute severity of illness as determined by the Pitt bacteremia score, mSOFA, and the proportion of patients with sepsis was comparable between the two groups. Overall, the majority of GN-BSI were community-acquired, the urinary tract was the most common source of infection, and *Escherichia coli* was the most common bloodstream isolate. In addition, since patients with major risk factors for antimicrobial resistance were excluded from the analysis, only eight patients (4%) in this cohort overall received inappropriate empirical antimicrobial therapy (Table 1). Antimicrobial susceptibility results of bloodstream isolates to commonly tested BSBL and fluoroquinolones are listed in Table 2. Charlson comorbidity score was the only variable that differed between the two treatment groups and was included in the logistic regression modelling the propensity of receiving empirical fluoroquinolone therapy.

Levofloxacin (54 patients; 73%) and ciprofloxacin (20; 27%) were the only fluoroquinolones used for empirical therapy of GN-BSI. Empirical BSBL included ceftriaxone (57; 39%), piperacillin/tazobactam (55; 37%), meropenem (17; 11%), cefepime (10; 7%), ertapenem (5; 3%), and others (4; 3%).

3.2. Clinical outcomes of patients with GN-BSI

Early treatment failure and 28-day mortality rates were comparable between the two groups (Table 3; Fig. 2). After adjustments for the propensity of receiving empirical fluoroquinolones in the respective multivariable models, there were no significant differences in early treatment failure (OR 0.82, 95% CI: 0.43–1.54, $P = 0.53$) or 28-day mortality (HR 0.74, 95% CI: 0.26–1.90, $P = 0.54$) in patients who received empirical fluoroquinolones relative to BSBL (Table 4).

Median HLOS was 6.1 and 7.1 days in the fluoroquinolone and BSBL groups, respectively ($P = 0.04$; Fig. 3). This difference remained statistically significant after adjustment for the

Table 1
Baseline demographics, clinical characteristics, and microbiology of bloodstream infections, based on empirical antimicrobial therapy.

Variable	Fluoroquinolones (*n* = 74)	BSBL (*n* = 148)	*P*-value
Age, median (IQR)	67 (56–80)	68 (55–79)	Matched
Female, *n* (%)	53 (72)	106 (72)	Matched
BSIMRS, median (IQR)	2 (0–4)	2 (0–4)	Matched
Cancer, *n* (%)	10 (14)	14 (9)	–
Liver cirrhosis, *n* (%)	3 (4)	7 (5)	–
High inoculum infection,[a] *n* (%)	23 (31)	40 (27)	–
Pitt bacteremia score, median (IQR)	1 (1–3)	1 (1–3)	–
mSOFA, median (IQR)	2 (1–4)	2 (1–3)	0.82
Sepsis, *n* (%)	26 (35)	55 (37)	0.77
Charlson comorbidity score, median (IQR)	2 (1–3)	1 (0–3)	0.10
Site of acquisition, *n* (%)			0.86
Community-acquired	54 (73)	103 (70)	–
Healthcare-associated	12 (16)	28 (19)	–
Hospital-acquired	8 (11)	17 (11)	–
Urinary source of infection, *n* (%)	49 (66)	103 (70)	0.61
Microbiology, *n* (%)			0.19
Escherichia coli	45 (61)	101 (68)	–
Klebsiella species	11 (15)	20 (14)	–
Proteus mirabilis	8 (11)	4 (3)	–
Other Enterobacteriaceae	8 (11)	18 (12)	–
Lactose non-fermenters	2 (3)	5 (3)	–
Inadequate source control, *n* (%)	1 (1)	2 (1)	0.99
Inappropriate empirical antimicrobial therapy, *n* (%)	5 (7)	3 (2)	0.12

BSBL, broad-spectrum beta-lactams; BSIMRS, bloodstream infection mortality risk score; IQR, interquartile range; mSOFA, modified sequential organ failure assessment.
[a] Source of bloodstream infection other than urinary tract or central venous catheter infection.

propensity of receiving empirical fluoroquinolones in the multivariable model (HR 0.73, 95% CI: 0.54–0.99, $P = 0.04$). Transition from intravenous to oral antimicrobial therapy occurred earlier in the fluoroquinolone than the BSBL group (median of 3.0 vs. 4.9 days, $P < 0.001$). There was no difference in 28-day mortality between the 37 patients transitioned from intravenous to oral fluoroquinolones within the first 3 days of BSI and the other 37 who remained on intravenous fluoroquinolones during the first 3 days of BSI (8.6% vs. 9.2%, log-rank $P = 0.93$).

4. Discussion

4.1. Impact of empirical antimicrobial therapy on outcomes

To our knowledge, this is the first study to compare effectiveness of fluoroquinolones to BSBL for empirical therapy of GN-BSI. Earlier studies demonstrated that ciprofloxacin was non-inferior to ceftazidime for empirical therapy of serious Gram-negative infections soon after introduction of the fluoroquinolone class to the antimicrobial arsenal [23,24]. However, replication of these results became impractical after the linear increase in fluoroquinolone resistance rates among Gram-negative bloodstream isolates [1–3]. A recent study suggested clinical benefit of appropriate empirical fluoroquinolone therapy over third-generation cephalosporins in a retrospective cohort of patients with community-onset BSI due to fluoroquinolone-susceptible Gram-negative bacilli [25]. However, application of study results in clinical practice was dependent on prospective identification of patients with BSI due to fluoroquinolone-susceptible bacteria at the time of the decision-making regarding empirical antimicrobial therapy. Recent advancements in clinical tools for prediction of antimicrobial resistance using patient-specific risk factors allowed precise estimation of the probability of fluoroquinolone resistance in Gram-negative bloodstream isolates [9,11]. The current study included only patients with low predicted risk of antimicrobial resistance at initial presentation and, predictably, over 90% had BSI due to fluoroquinolone-susceptible Gram-negative bacilli. The study results provide an alternative empirical antimicrobial option to BSBL in patients with GN-BSI who may not be eligible for beta-lactam therapy. This includes patients who had prior adverse events to both penicillins and cephalosporins and those with recent major penicillin allergies such as anaphylaxis or angioedema. In the absence of major risk factors for antimicrobial resistance, empirical fluoroquinolones had comparable early treatment failure and 28-day mortality to BSBL.

Table 2
Antimicrobial susceptibility testing results of bloodstream isolates in the two treatment groups.

Antimicrobial agent	Fluoroquinolones (*n* = 74)	BSBL (*n* = 148)
Piperacillin/tazobactam	70/72 (97)	143/145 (99)
Ceftazidime	72/73 (99)	145 (98)
Cefepime	73 (99)	147 (99)
Meropenem	74 (100)	146 (99)
Ciprofloxacin	69 (93)	137 (93)

Data represent number of susceptible isolates (percentage of susceptible isolates) if all isolates were tested; otherwise number of susceptible isolates/number of isolates tested (percentage of susceptible isolates).
BSBL, broad-spectrum beta-lactams.

4.2. Early transition from intravenous to oral antimicrobial therapy

The study also has clinical implications in early transition from intravenous to oral antimicrobial therapy. Fluoroquinolones remain the most frequently used oral antimicrobial agents in patients with GN-BSI. In a recent multicentre cohort and a randomized clinical trial, 70% and 74% of patients transitioned from intravenous to oral therapy for Enterobacteriaceae and GN-BSI, respectively, received oral fluoroquinolones [7,26]. However, transitioning from intravenous to oral antimicrobial therapy often occurred after 72 h of GN-BSI to ensure that bloodstream isolates were susceptible to oral antimicrobial regimen [5–8]. In the current study, using simple clinical criteria for risk stratification of antimicrobial resistance allowed early transition from intravenous to oral antimicrobial therapy within 3 days of GN-BSI in one-half of patients in the fluoroquinolone group. This early and smooth transition from intravenous to oral therapy likely contributed to shorter HLOS in the fluoroquinolone group than in the BSBL group. This was consistent with the results of prior cohort studies that demonstrated an association between transition from intravenous to oral antimicrobial therapy and shorter HLOS [6–8]. However, to

Table 3
Summary of primary and secondary outcomes of patients with Gram-negative bloodstream infections by treatment group.

Outcome	Fluoroquinolones (*n* = 74)	BSBL (*n* = 148)	*P*-value
Early treatment failure, *n* (%)	20 (27)	44 (30)	0.67
Death within 72 h of BSI	1 (1)	6 (4)	–
ECFC ≥2 from 72 to 96 h of BSI	19 (26)	38 (26)	–
Hypotension	12 (16)	22 (15)	–
Tachycardia	18 (24)	44 (30)	–
Respiratory failure	15 (20)	30 (20)	–
Altered mental status	8 (11)	19 (13)	–
Leucocytosis	14 (19)	28 (19)	–
28-day mortality[a]	8.9%	9.7%	0.79
Median HLOS in days[a]	6.1	7.1	0.04

BSBL, broad-spectrum beta-lactams; BSI, bloodstream infection; ECFC, early clinical failure criteria; HLOS, hospital length of stay.
[a] Results were obtained from respective Kaplan–Meier curves.

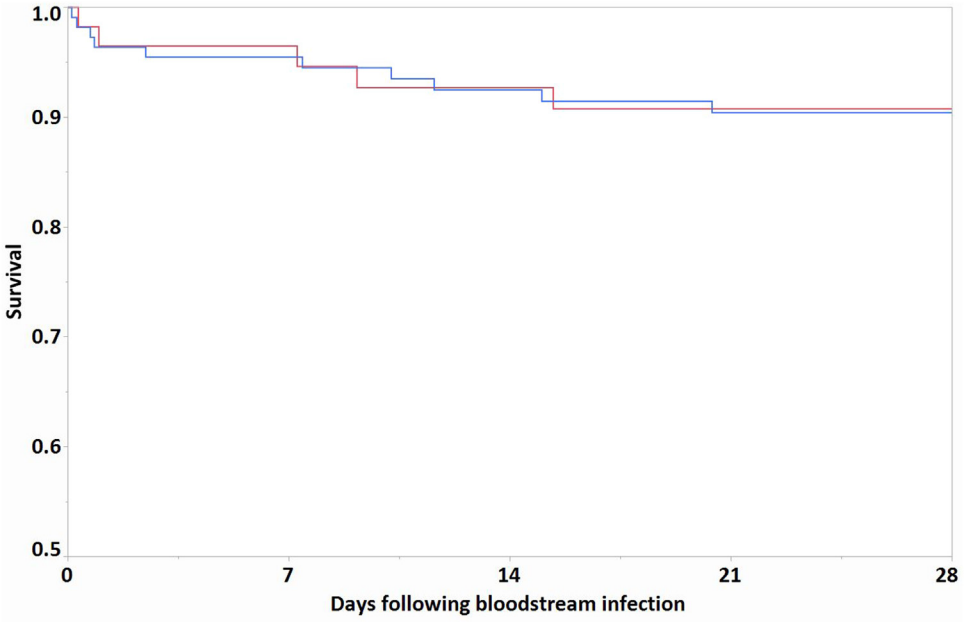

Fig. 2. Mortality in patients with Gram-negative bloodstream infection by empirical antimicrobial therapy. Red line indicates fluoroquinolones and blue line indicates broad-spectrum beta-lactams. Log-rank *P* = 0.79.

Table 4
Univariable and multivariable model results for primary and secondary outcomes of study.

Outcome	Univariable model			Multivariable model[a]		
	OR/HR	(95% CI)	*P*-value	OR/HR	(95% CI)	*P*-value
Early treatment failure	0.88	(0.50–1.63)	0.68	0.82	(0.43–1.54)	0.53
28-day mortality	0.88	(0.31–2.23)	0.79	0.74	(0.26–1.90)	0.54
Hospital length of stay	0.74	(0.55–1.00)	0.047	0.73	(0.54–0.99)	0.043

OR and HR in patients receiving empirical fluoroquinolones relative to broad-spectrum beta-lactams.
CI, confidence interval; HR, hazards ratio; OR, odds ratio.
[a] After adjustment for the propensity of receiving empirical fluoroquinolones based on Charlson comorbidity score.

our knowledge, this is the first study to demonstrate feasibility of intravenous to oral transition of antimicrobial therapy within 3 days of GN-BSI. It was reassuring that early transition from intravenous to oral fluoroquinolones within 3 days of BSI was not associated with increased 28-day mortality. This approach requires healthcare providers to be familiar with local risk factors for antimicrobial resistance and confident in estimating the probability of antimicrobial resistance rates using available resources. Utilization of novel methods for rapid phenotypic antimicrobial susceptibility testing using morphokinetic cellular analysis provides an arguably more precise, albeit more expensive, alternative to clinical risk assessment tools for prediction of antimicrobial resistance [27–29]. Future larger trials examining early transition from intravenous to oral antimicrobial therapy within 3 days of GN-BSI would yield valuable results.

4.3. Strengths and limitations

Matching by predicted prognosis using the BSIMRS represents the major strength of this study as it allows examination of patients with comparable baseline prognosis prior to initiation of empirical antimicrobial therapy. The study has the following limitation. First,

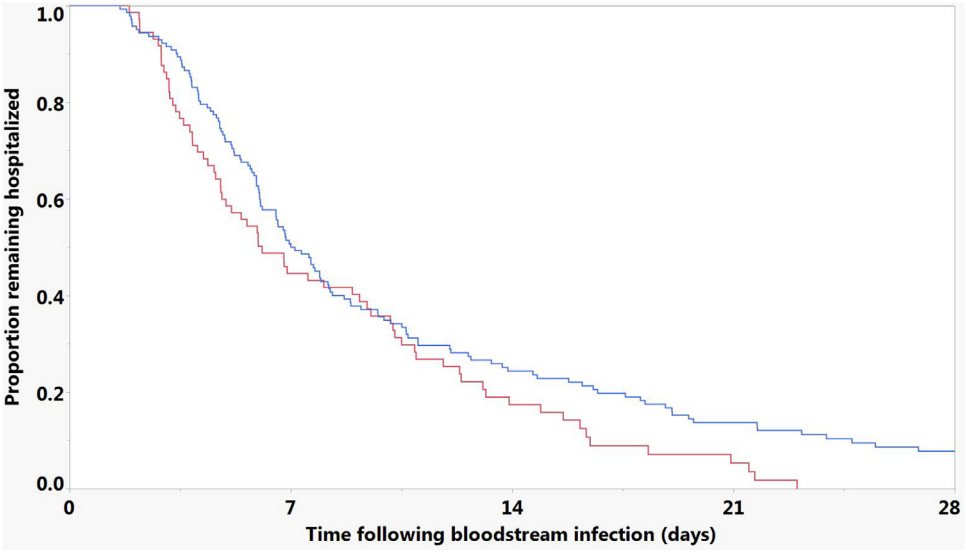

Fig. 3. Hospital length of stay following Gram-negative bloodstream infection by empirical antimicrobial therapy. Red line indicates fluoroquinolones and blue line indicates broad-spectrum beta-lactams. Log-rank $P = 0.04$.

it shares common limitations of retrospective cohorts, including the potential of not accounting for unknown confounders. Second, the number of patients who received empirical fluoroquinolone therapy during the study period was relatively small. This is conceivably because the non-stratified use of empirical fluoroquinolone therapy for GN-BSI has been discouraged due to increasing antimicrobial resistance rates. However, the study had adequate power to examine the primary outcome of early treatment failure. Third, the study was conducted at two hospitals within the same healthcare system. The antimicrobial stewardship and support team provided real-time recommendations regarding empirical antimicrobial therapy and oral switch options in patients with GN-BSI. These results may not be generalizable to settings with limited access to infectious diseases specialists and antimicrobial stewardship expertise in prediction of antimicrobial resistance.

5. Conclusion

In patients with low predicted risk of antimicrobial resistance, empirical fluoroquinolone therapy for GN-BSI had comparable early treatment failure and 28-day mortality to BSBL. Early transition from intravenous to oral antimicrobial therapy likely contributed to shorter HLOS in the fluoroquinolone group than in the BSBL group.

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Competing interests

BB: FreeCE.com, content developer and speaker; ALK Abello, Inc., research grant support recipient and consultant; Melinta Therapeutics, consultant. All other authors declare no competing interests.

Ethical approval

The study was approved by Prisma Health-Midlands Institutional Review Board (Columbia, SC, USA).

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