

VOLUME 03 ISSUE 02 (2024)



AMERICAN JOURNAL OF
**MEDICAL SCIENCE
AND INNOVATION**
(AJMSI)

ISSN: 2836-8509 (ONLINE)



PUBLISHED BY

E-PALLI PUBLISHERS, DELAWARE, USA

Gram-Negative Bacteremia: Epidemiology and Antimicrobial Resistance in Qatar

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Article Information

Received: September 05, 2024

Accepted: October 02, 2024

Published: October 05, 2024

Keywords

Antimicrobial Resistance, Clinical Outcomes, Epidemiology, ESBL-Producing Bacteria, Gram-Negative Bacteremia

ABSTRACT

One of the major causes of morbidity and mortality in hospitalised patients is the presence of gram-negative bacteremia (GNB) in blood. The developed resistance among the bacteria poses a significant challenge for treatment. The study aimed to identify the gram-negative patient's epidemiological risk factors, antimicrobial susceptibility patterns, and clinical outcomes. A retrospective observational study of adult in-patients with gram-negative bacteremia was conducted between January 2019 and December 2020 in the 320-bed general hospital in Qatar. Data on demographics, antimicrobial resistance, source of infection, and treatment were collected. The primary outcomes were patients' cure, death, or relapse. Total of 357 patients were identified with bacteremia, the most common sources being urinary tract infections (39.6%), intra-abdominal infections (28%), and lower respiratory tract infections (9%). The mean duration of the intravenous and oral antibiotics administration was 14 days. Surgical source control was performed in 35.7% of patients. Common pathogens were *Escherichia coli* (47.2%), *Klebsiella pneumoniae* (16.4%), *Salmonella enterica* serotype Typhi (10.6%), and *Pseudomonas aeruginosa* (7.8%). 67.32% fully susceptible strains, 31.56% extended-spectrum beta-lactamase (ESBL) producing bacteria, and 1.11% multidrug-resistant organisms (MDROs) were among the isolates. Most infections (68%) were cured, but 5% had recurrence within 90 days of admission. Infection-related mortality was 8%, and death due to non-infectious causes was 2%. In conclusion, Gram-negative BSIs are severe infections with increasing antimicrobial resistance, primarily caused by ESBL-producing bacteria. High mortality rates are linked to diabetes, age, and hospitalisation, necessitating antibiotic treatment optimisation.

INTRODUCTION

Gram-negative bacteria are known to cause a range of infections, including urinary tract infections, biliary infections, pneumonia, and primary and secondary bloodstream infections (Gajdacs *et al.*, 2019; Kim & Park, 2018; Kwiecińska-Piróg *et al.*, 2018). Factors that predispose to these infections include extreme age, comorbidities such as diabetes mellitus, immunosuppression, prior use of antimicrobials, medical device usage, and invasive interventions such as surgery, nosocomial acquisition, and duration of stay, even though without a predisposing factor, the infection may also arise (Gajdacs *et al.*, 2019). One of the major factors contributing to the mortality and morbidity of hospitalised patients is gram-negative bacteremia (GNB). These patients require prompt diagnosis and appropriate antibiotic therapy. The initiation of appropriate antibiotics can reduce mortality, treatment failure, and length of stay, highlighting the importance of broad-spectrum empirical therapy, diagnostic stewardship, and rapid diagnostics for early and timely identification (Bassetti *et al.*, 2020; Gajdacs *et al.*, 2019). Conflicting observations have resulted in uncertainty concerning the optimum duration of antibiotic therapy for bacteremia caused by gram-negative infections. Many

believe gram-negative bacteremia patients should be treated with a 10-14-day intravenous antibiotics course to prevent serious sequelae, such as abscess formation and relapse (Turjeman *et al.*, 2023). Recently, Lee *et al.* (2019) and Yahav *et al.* (2019) have suggested that short therapy courses are adequate for uncomplicated bacteremia (Lee *et al.*, 2019; Yahav *et al.*, 2019). The emerging resistance among these bacteria significantly challenges healthcare delivery (Iskandar *et al.*, 2021). Infections by antimicrobial-resistant organisms, particularly multidrug-resistant organisms (De Waele *et al.*, 2018), could result in treatment failure, increased morbidity and mortality, increased medical costs, prolonged hospital stays, and increased socioeconomic burden (Iskandar *et al.*, 2021; Kitaya *et al.*, 2023).

In high resistance rates, selecting appropriate empiric antibiotic treatment for suspected gram-negative infections is difficult (Fitzpatrick *et al.*, 2016). Inappropriate empirical antimicrobial therapy has been shown to predict death in critically ill patients (Turjeman *et al.*, 2023). Furthermore, prolonged antimicrobial exposure is associated with adverse effects, increased rates of *Clostridioides difficile* infection, antimicrobial resistance, and longer hospital stays (Dyer *et al.*, 2019).

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Different centres vary depending on the patient population, immune status, infection control precautions, and antimicrobial use (Spellberg & Rice, 2019). Analysis of local trends and epidemiology is necessary to optimise empirical antibiotic treatment (Yahav *et al.*, 2019). If indicated, appropriate antimicrobial therapy with source control is warranted to achieve optimal outcomes (Turjeman *et al.*, 2023). The study aims to identify the local epidemiologically predisposing factors, antimicrobial susceptibility patterns, and clinical outcomes in adult patients with gram-negative bacteremia, focusing on factors associated with morbidity and mortality.

MATERIALS AND METHODS

Study Design and Selection Criteria

A retrospective cohort study was conducted on in-patient adults with gram-negative bacteremia between January 2019 and December 2020 in a 320-bed general hospital in Qatar. All adult patients who presented with gram-negative bacteremia during the study period based on positive blood cultures were identified retrospectively from the Microbiology Lab through hospital electronic records. Pediatric patients (aged <14 years) and transit passengers were excluded from the study. Samples considered contaminants, as determined by the clinical picture and subsequent management, were also not included.

A Microbiology database was used to record antimicrobial susceptibility testing current guidelines from the Clinical and Laboratory Standards Institute (CLSI) (Iskandar *et al.*, 2021). The hospital's electronic patient record system was used to capture all clinical data related to these patients. In contrast, the demographic details, including age, sex, comorbidities (immunosuppression, malignancy, pregnancy, renal disease, diabetes, and hypertension), and clinical presentation, were also recorded. A need for admission to the critical care unit was used to assess the severity of infection. The probable source of infection, persistence of bacteremia beyond the first blood culture, and therapeutic options with intravenous antibiotics alone or combined with source control (incision and drainage of abscesses, stent insertion) were examined. The choice of antibiotics and duration of treatment, including changes made according to sensitivity, were also recorded. Clinical outcomes were gauged as cure, death, or infection recurrence within 90 days of admission. Any subsequent development of alert organisms such as *Clostridium difficile* infection or the emergence of multidrug-resistant microorganisms 90 days after admission was also monitored. Multidrug resistance (MDR) was defined as resistance to at least one agent from three or more antimicrobial classes (Yezli *et al.*, 2014).

Ethical Approval

This study was approved by the Institutional Review Board (IRB) and Medical Research and Ethics Committee Hamad Medical Corporation (Protocol ID MRC-01-21-259). However, this retrospective cohort review did not obtain individual patient consent.

Statistical Analysis

Statistical analysis was conducted on 358 patients using the Sata/Se 14.2. The study analysed epidemiological data, including descriptive statistics and continuous and categorical variables. Categorical variables were presented as counts and percentages, whereas normal continuous variables are expressed as means and standard deviations, and non-normal variables are presented as medians and interquartile ranges (IQR). The Shapiro-Wilk test and visual inspection of histograms were employed to assess the normality of the data. The student's t-test was applied to normal outcomes, the Mann-Whitney test was applied to non-normal outcomes, and the chi-square test was used for categorical variables. Survival analysis was performed using Kaplan-Meier survival curves and the log-rank test to assess the differences between the groups for variables associated with mortality based on univariate analysis.

RESULTS AND DISCUSSIONS

The demographic and clinical characteristics of the cohort with gram-negative bacteremia were analysed, with a total of 358 patients included in the study. Among these patients, the majority (218, 60.8%) were male, with a mean age of 51. Table 1 describes the comorbidities observed in the study population. Notably, diabetes mellitus emerged as a significant confounding factor. Patients' demographic and clinical profiles were stratified based on their diabetes status, resulting in 197 non-diabetic patients (Non-DM) and 160 diabetes patients (DM). The non-diabetic group exhibited a significantly younger age than the diabetic group (median ages of 42.5 vs. 60, respectively, $p < 0.001$). Furthermore, hypertension, end-stage renal disease on hemodialysis, and chronic kidney disease were more prevalent in the diabetic group compared to the non-diabetic group ($p < 0.001$ for all). Although the length of hospital stay did not differ significantly between the two groups ($p = 0.94$), primary bacteremia was more common in the non-diabetic group ($p = 0.038$). Bacterial isolates also showed significant differences in prevalence, particularly with *E. coli*, Klebsiella, and Salmonella Typhi. Additionally, the source of bacteremia varied significantly between the groups, with urinary tract and intra-abdominal infections being prominent in both. Antibiotic resistance did not notably differ between the groups ($p = 0.49$), As shown in Table 1.

Table 1: Baseline characteristics of the study population by diabetes status

	Non-DM (n = 197)	DM (n = 160)	
Demographics			
Age (Wilcoxon rank)	42.00 (28.00-54.00)	60.00 (49.50-70.00)	<0.001

Male	128 (64.65%)	90 (56.25%)	0.093
Comorbidities			
HTN	37 (18.76%)	115 (71.88%)	<0.001
ESRD HD	07 (3.55%)	25 (15.63%)	<0.001
CKD	11 (5.58%)	33 (20.63%)	<0.001
Malignancy	26 (13.20%)	9 (5.63%)	0.012
COPD/Asthma	12 (6.09%)	12 (7.50%)	0.59
HIV	0 (0.00%)	1 (0.63%)	
IHD	7 (3.55%)	38 (23.75%)	<0.001
HF	10 (5.08%)	13 (8.13%)	0.24
Liver disease	9 (4.57%)	13 (8.13%)	0.16
Pregnant females (Fisher's exact)	7 (10.14 %)	1 (1.43 %)	0.063
Valvular disease (Fisher's exact)	3 (1.52%)	10 (6.25%)	0.017
Cystic fibrosis	0 (0%)	0 (0%)	
Inflammatory bowel disease (Fisher's exact)	0 (0.00%)	1 (0.63%)	0.45
Tuberculosis	1 (0.51%)	0 (0.00%)	1
Immunosuppressive treatment	15 (7.61%)	9 (5.63%)	0.46
Long hospital stays	10 (5.08%)	12 (7.50%)	0.34
Complicated bacteremia	51 (25.89%)	53 (33.13%)	0.16
Persistence	13 (6.60%)	5 (3.13%)	0.15
Intubated	31 (15.74%)	29 (18.13%)	0.56
ICU	52 (26.40%)	39 (24.38%)	0.61
Readmission	25 (12.69%)	23 (14.37%)	0.88
Length of stay (Wilcoxon rank)	35.00 (16.00-44.00)	33.00 (12.00-46.00)	0.94
Emergence	7 (3.55%)	15 (9.38%)	0.05
C. diff	2 (1.02%)	0 (0.00%)	0.63
Source control			0.046
Yes	81 (41.12%)	47 (29.38%)	
Unknown	36 (18.27%)	42 (26.25%)	
Abs Previous	36 (18.27%)	63 (39.38%)	<0.001
Completed IV			0.008
In-patient	128 (64.97%)	106 (66.25%)	
MHS	17 (8.63%)	29 (18.13%)	
OPAT	47 (23.86%)	24 (15.00%)	
Unknown	5 (2.54%)	1 (0.63%)	
Microbiology			
Primary bacteremia	75 (38.07%)	44 (27.50%)	0.038
Community-acquired bacteremia	157 (79.70%)	131 (81.88%)	
Bacterial isolates			0.004
<i>Acinetobacter</i>	3 (1.52%)	5 (3.13%)	
<i>Brucella</i>	6 (3.03%)	2 (1.25%)	
<i>Citrobacter</i>	1 (0.51%)	1 (0.63%)	
<i>E. coli</i>	90 (45.45%)	79 (49.38%)	
<i>Enterobacter cloacae</i>	6 (3.03%)	2 (1.25%)	
<i>Klebsiella</i>	28 (14.14%)	31 (19.38%)	
<i>Non-typhoidal Salmonella</i>	5 (2.53%)	0 (0.00%)	
<i>Proteus</i>	2 (1.01%)	4 (2.50%)	
<i>Pseudomonas</i>	12 (6.06%)	15 (9.38%)	

<i>Salmonella Typhi</i>	33 (16.67%)	5 (3.13%)	
<i>Serratia</i>	5 (2.53%)	6 (3.75%)	
Unidentified anaerobic <i>Bacilli</i>	0 (0.00%)	1 (0.63%)	
<i>Pseudomonas</i>	1 (0.51%)	0 (0.00%)	
<i>Stenotrophomonas</i>	0 (0.00%)	1 (0.63%)	
Missing	6 (3.03%)	8 (5.00%)	
Resistance			0.49
ESBL	57 (28.93%)	46 (28.75%)	
MDR	9 (4.57%)	12 (7.50%)	
None	131 (66.50%)	102 (63.75%)	
Source bacteremia (Fisher's exact)			0.004
Urinary tract infection	71 (36.04%)	71 (44.38%)	
Bone and soft tissue infection	7 (3.55%)	15 (9.38%)	
Burn wound infection	3 (1.52%)	0 (0.00%)	
Cardiovascular infection	1 (0.51%)	2 (1.25%)	
intra-abdominal infection	70 (35.53%)	31 (19.38%)	
Line related infection	4 (2.03%)	7 (4.38%)	
Lower respiratory tract infection	20 (10.15%)	17 (10.63%)	
Unknown	20 (10.15%)	17 (10.63%)	
Surgical site infection	1 (0.51%)	0 (0.00%)	

Figure 1 shows that 68% of patients with gram-negative bloodstream infections (GNB) successfully recovered from sepsis, but 8% succumbed to sepsis, 5% experienced recurrence, and 6% died from unrelated causes. 5% showed multidrug-resistant organisms, indicating

antimicrobial resistance. 2% experienced prolonged bacteremia, and 6% died from unknown causes. These findings highlight the complexity of GNB management and the need for comprehensive strategies to prevent adverse events.

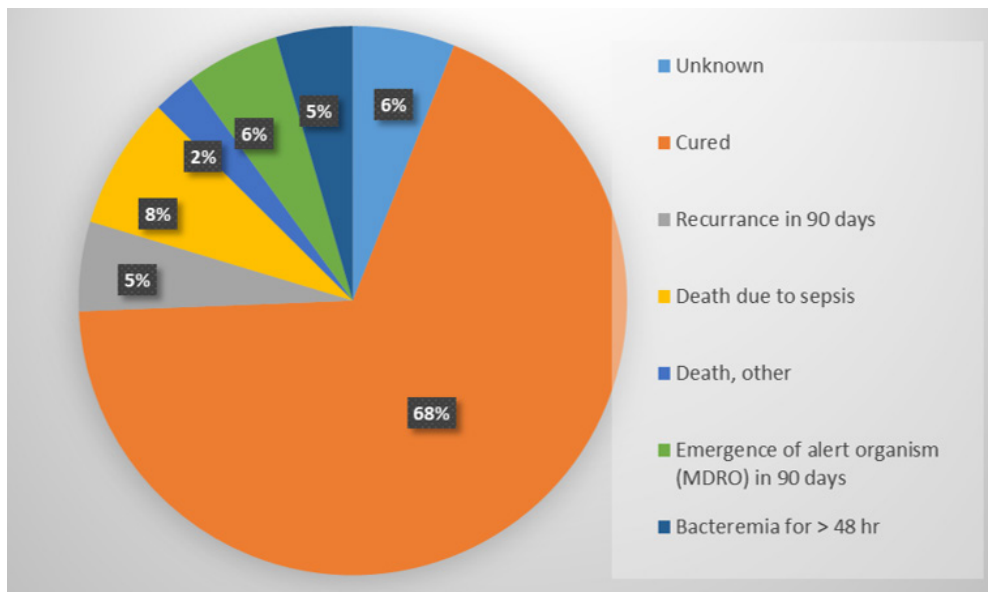


Figure 1: The primary clinical outcomes of this study are shown in chart

The duration of treatment with intravenous antibiotics revealed that most patients underwent a short course of intravenous therapy. Specifically, more than 70% of patients received treatment lasting less than 10 days,

which suggests a trend towards shorter intravenous antibiotic therapy durations in managing gram-negative bacteremia cases, as shown in Table 2.

Table 2: Intravenous (IV) treatment duration – intervals

Duration of IV treatment (days)	Counts	Percentages %
<7	161	44.97
7 to 10	100	27.93
11 to 14	54	15.08
>14	43	12.01
Sum	358	100

Figure 2 shows the distribution of gram-negative bacteremia by infection site. Urinary tract infections are most common (45%), followed by intra-abdominal infections (40%) and lower respiratory tract infections (15%). A notable proportion (10%) has an unknown infection site. Other sites include bone and soft

tissue infections (5%), line-related infections (2.5%), cardiovascular infections (1%), and miscellaneous sources (2.5%). This breakdown underscores the varied origins of gram-negative bacteremia, emphasizing the need for tailored treatment strategies based on infection site specificity.

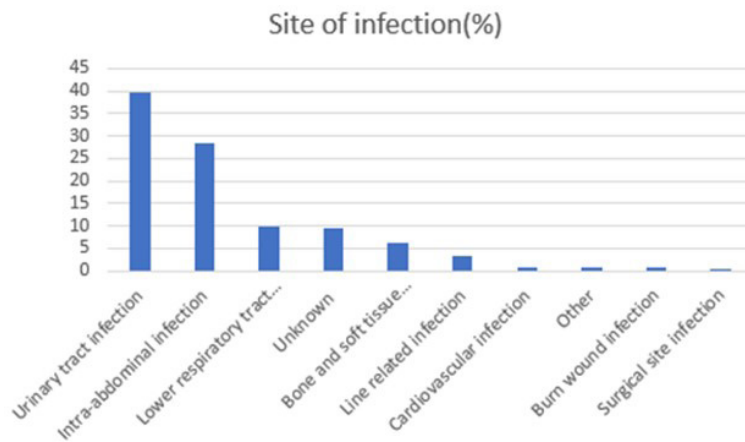


Figure 2: Epidemiology of gram-negative bacteremia

Escherichia coli was the most frequently identified organism, accounting for 47.2% of cases, followed by *Klebsiella pneumoniae* (16.4%), *Salmonella enterica* serotype Typhi (10.6%), and *Pseudomonas aeruginosa* (7.8%). Other less common organisms included *Serratia marcescens* (3%), *Acinetobacter baumannii* (2.2%), *Brucella sp.* (2.2%), non-typhoidal *Salmonella* (1.3%), *Citrobacter sp.* (0.5%), and various others (8.3%). These

findings detail the characteristics of gram-negative bacteria isolated in the study, highlighting the prevalence of different species contributing to persistent bacteremia cases. Additionally, the mean duration of antimicrobial treatment, including intravenous and oral administration, was 14.6 days, with intravenous antibiotics specifically administered for an average duration of 5.4 days, as shown in Table 3.

Table 3: Organisms isolated in persistent bacteremia

Organism	Count (out of 18)	Percentage %
<i>E. coli</i>	4	22.22
<i>Klebsiella sp.</i>	5	27.77
<i>Enterobacter cloacae</i>	1	5.55
<i>Pseudomonas sp.</i>	2	11.11
<i>Salmonella typhi</i>	3	16.66
<i>Proteus sp.</i>	1	5.55
<i>Stenotrophomonas maltophilia</i>	1	5.55
<i>Achromobacter sp.</i>	1	5.55

As illustrated in Figure 3, gram-negative bacteremia arises from various sources within the body. The most prevalent infection sites of cases originating in the urinary tract are evident. Intra-abdominal infections and lower respiratory

tract infections follow this. It is crucial to note that these percentages may not match the original figure exactly due to potential rounding errors.

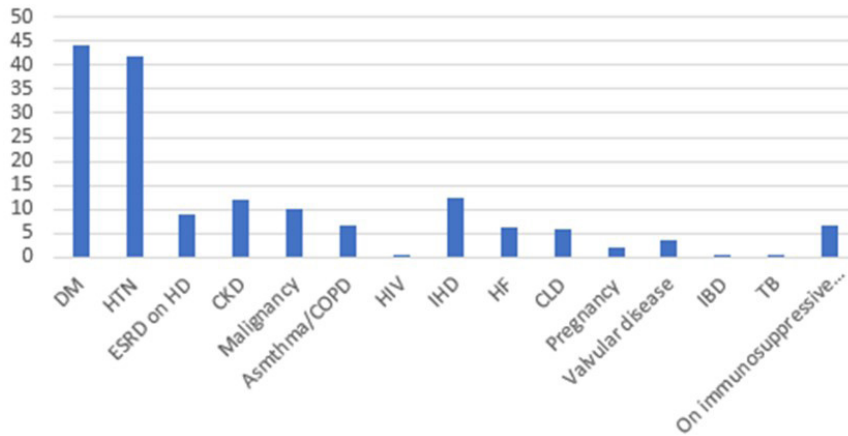


Figure 3: Common sites of infection in gram-negative bacteremia cases

There were four cases of multidrug-resistant organisms (MDROs), two *Klebsiella pneumoniae* carbapenemase-producing Enterobacteriaceae (KPC), and two New Delhi metallo-beta-lactamase-1 (NMD-1). Extended-spectrum beta-lactamase-producing organisms (ESBL) constituted 31.56% (113) cases. Antibiotic collateral damage was noted as the emergence of MDRO in 90 days in 22 patients (6.1%) and *Clostridium difficile* in two patients (0.5%). Persistent bacteremia was reported in 18 patients (5%), out of which nine (50%) had intra-abdominal infections, three had soft tissue infections (16.7%), two had lower respiratory tract infections (11.1%), two had urinary tract infections (11.1%), one had cardiovascular infection (5.5%), and one had line-related infection (5.5%), as shown in Table 4.

Table 4: Description of bacterial isolates

Organisms	Count	Percentage (%)
Multidrug-resistant organisms (MDROs)	4	1.11
Extended-spectrum beta-lactamase-producing organisms (ESBL)	113	31.56
Sensitive strains	241	67.32
Single microbe	336	93.85
Polymicrobial	22	6.14

Figure 4 illustrates the distribution of gram-negative bacteremia cases by different bacterial types. The listed bacteria include *Escherichia coli*, *Klebsiella pneumoniae*, *Salmonella typhi*, *Pseudomonas*, *Serratia*, *Acinetobacter*, non-typhoidal *Salmonella*, and *Citrobacter*. The X-axis

represents the percentage of cases for each bacterial type. This graph provides insights into the prevalence of various bacterial species causing gram-negative bacteremia, which is essential for understanding the epidemiology and guiding treatment approaches for these infections.

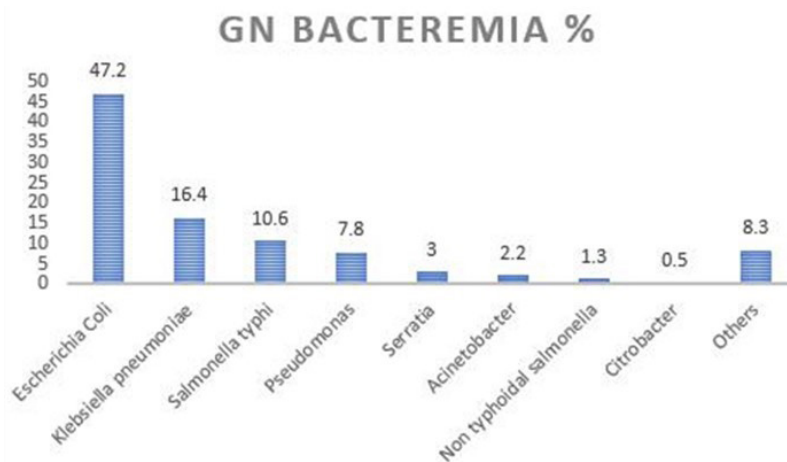


Figure 4: Comorbidities in gram-negative bacteremia cases

Table 5 illustrates the management of source control in patients with persistent bacteremia. Among 18 patients with persistent bacteremia, source control was performed in seven cases, accounting for 38.9% of the cohort.

Conversely, five patients (27.8%) did not require source control. In contrast, source control was deemed necessary in six cases (33.3%) but was not carried out due to factors such as the patient's unstable condition or inaccessible sites.

Table 5: Comorbidities of Study Population

Comorbidity	Number	Percentage (%)
Diabetes mellitus	160	44.69
Hypertension	152	42.45
The end-stage renal disease of dialysis	32	8.93
Chronic kidney disease	44	12.29
Malignancy	36	10.05
Asthma/Chronic Obstructive Pulmonary Disease	24	6.70
Human Immunodeficiency Virus	1	0.27
Ischemic heart disease	45	12.56
Heart failure	23	6.42
Chronic liver disease	22	6.14
Pregnancy	8	2.23
Valvular disease	13	3.63
Cystic fibrosis	0	0
Inflammatory bowel disease	1	0.27
Tuberculosis	1	0.27
Immunosuppressive treatment	24	6.70

Figure 5 presents the survival probability comparison between diabetic and non-diabetic patients following a positive culture. According to the graph, patients without diabetes have a better chance of surviving than those with the disease. This observation underscores the potential impact of diabetes as a comorbidity on

patient outcomes in cases of gram-negative bacteremia. Understanding such differences in survival probabilities can inform clinical decision-making and highlight the importance of tailored management strategies for patients with diabetes who develop gram-negative bacteremia.

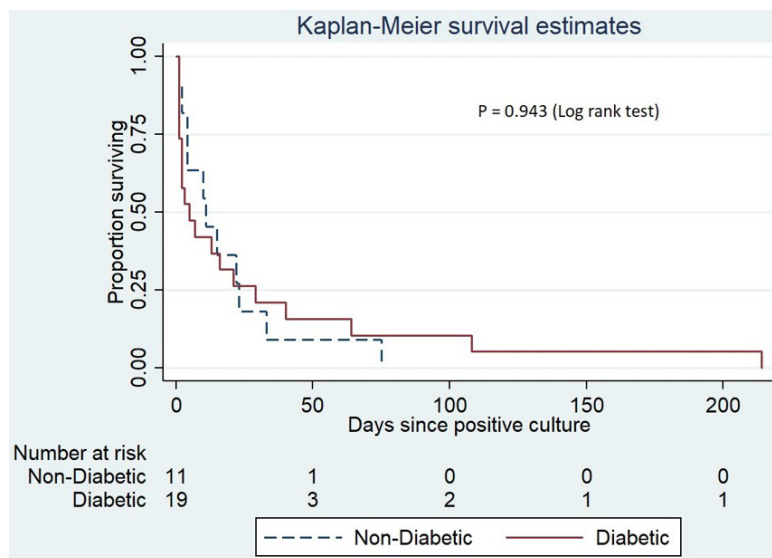


Figure 5: Kaplan-Meier survival analysis denoting survival probability of diabetic and non-diabetic groups

Table 6 presents the duration of antibiotic treatment in diabetic (DM) and non-diabetic (non-DM) patient groups with gram-negative bacteremia. Statistical analysis revealed no significant difference in the duration of

antibiotic treatment between the two groups ($p=0.617$). Most patients in both groups received antibiotics for more than 14 days, with 63 (31.98%) in the DM group and 52 (32.5%) in the non-DM group. Interestingly, a

slightly higher percentage of diabetic patients (10.63%) received antibiotics for less than 7 days compared to non-diabetic patients (8.63%). Moreover, a somewhat

higher proportion of diabetic patients (35.63%) received antibiotics for 11 to 14 days compared to non-diabetic patients (32.49%).

Table 6: Total duration of antibiotic treatment in diabetic and non-diabetic patients

Total duration of treatment (days)	Non-DM (n=197)		DM (n=160)	
	Count	Percentages %	Count	Percentages %
Less than 7 days	17	8.63	17	10.63
7 to 10 days	53	26.90	34	21.25
11 to 14 days	64	32.49	57	35.63
More than 14 days	63	31.98	52	32.5
P-value = 0.617				

Univariate analysis of recurrence at 90 days, cure rate, and death due to sepsis showed a significant difference between the groups ($p=0.037$, $p=0.09$, $p=0.052$, respectively). The sepsis outcomes comparison revealed that diabetic patients had a higher death risk due to

sepsis (11.88%) and recurrence within 90 days (8.75%) compared to non-diabetic patients. Additionally, the cure rate is less (69.38%) in diabetic patients than in non-diabetic patients (81.73%), as shown in Table 7.

Table 7: Univariate analysis of outcomes in diabetic and non-diabetic patients

Outcome (Fisher's exact)	Non-DM (n=197)	DM (n=160)	P-value
Death due to sepsis	11 (5.58%)	19 (11.88%)	0.052
Recurrence in 90 days	7 (3.55%)	14 (8.75%)	0.037
Cured	161 (81.73%)	111 (69.38%)	0.009

Age, treatment duration of fewer than seven days, and hospital-acquired infections showed a significant association with higher mortality in gram-negative bacteremia in the multivariate analysis (OR=1.040, $p=0.014$), (OR=20.030, $p=0.001$), (OR=3.517, $p=0.020$) respectively. Conversely, the presence of *E. coli* and UTI

as sources of infection was not significantly associated with mortality due to sepsis. Kaplan-Meier survival analysis was used to assess the survival probability of the diabetic and non-diabetic groups. The log-rank test result was insignificant ($p=0.934$), as shown in Table 8.

Table 8: Multivariate analysis of factors associated with mortality in gram-negative bacteremia patients adjusting for baseline characteristics

Variable	OR	p-value	95% Confidence Interval	
Age	1.040	0.014	1.008	1.072
Male	1.609	0.448	0.471	5.496
DM	1.008	0.990	0.314	5.496
HTN	4.060	0.056	0.967	17.049
ESRD/HD	1.237	0.756	0.324	4.716
Less than 7 days of treatment	20.030	<0.001	5.454	75.038
Hospital-acquired	3.517	0.020	1.217	10.168
Secondary	1.394	0.559	0.457	4.253
MDR	0.588	0.547	0.104	3.309
<i>E. coli</i>	0.457	0.192	0.141	1.482
UTI - a source of infection	0.043	0.007	0.004	0.040

Discussion

GNB bloodstream infections pose a serious health problem globally and in the Middle East, where antimicrobial resistance is rising (Inam *et al.*, 2023). Several studies have been conducted in this region to understand this condition's epidemiology and risk factors.

The emergence of antimicrobial resistance (AMR) has been the top agenda item for the past four years for the Gulf Cooperation Council Centre for Infection Control (GCC-IC) (Al Muhairi *et al.*, 2019). A previous study on the epidemiology of all bacteremia patients in Qatar found 452 cases of bacteremia with 63% gram-

negative organisms (Borgio *et al.*, 2021), with *Escherichia coli* as the most common isolate. The present study also found *E. coli* to be the predominant bacterium (47.2%), followed by *Klebsiella pneumoniae* (16.4%). Many cases of Salmonella bloodstream infections (10.6%) in our centre were identified mainly as travellers or immigrants from Southeast Asia. *Salmonella typhi* was 10.6%, and non-typhoidal Salmonella constituted 1.3% of cases. An earlier study by Qatar found that 97% of patients had a history of travel to endemic areas (Ahmedullah *et al.*, 2018). *Salmonella typhi* isolates from the present study centre demonstrated high levels of resistance to ciprofloxacin (40%) but were susceptible to ceftriaxone. Among the cases, the *Brucella sp.* was identified in eight patients (2.2 %). In the Middle East and North Africa (MENA) region, brucellosis is not uncommon as a blood culture isolate (Wareth *et al.*, 2022). Usually, there is a history of exposure to cattle and camels, either through occupational exposure or consumption of dairy products. MDROs and ESBL-producing isolates comprised 34% of the samples, while the rest were sensitive strains (66%). Previous studies also found a higher prevalence of ESBL-producing *E. coli* and *Klebsiella pneumoniae* (55.7%) than present findings (Sid Ahmed *et al.*, 2023), which indicates the implementation of antimicrobial stewardship practices and monitoring the appropriateness of antimicrobials and their consumption. In addition, previous studies from Qatar reported 4.4 % MDR isolates of *Pseudomonas aeruginosa* (*P. aeruginosa*) (Ahmed *et al.*, 2019); however, out of 28 patients with *P. aeruginosa* bloodstream infection (7.8%), only 2 patients (0.56%) were multidrug-resistant, which is in contrast to studies from Saudi Arabia with a high prevalence of multidrug-resistant (MDR) bacteria, with more than 50% of the isolates resistant to at least one antimicrobial agent (Yezli *et al.*, 2014). Although *P. aeruginosa* remains susceptible to carbapenems, quinolones, and aminoglycosides in most centres in Saudi Arabia, its resistance is still on the rise. Similarly, Enterobacteriaceae, *Escherichia coli*, *Klebsiella pneumoniae*, and Enterobacter sp. AMR is increasing, especially in gram-negative infections in the Middle East (Sid Ahmed *et al.*, 2023). Prior use of antimicrobials is an established independent risk factor for the emergence of MDROs (Ahmed *et al.*, 2019). In Qatar, about half of the cases of *Klebsiella pneumoniae* are reported as extended-spectrum β -lactamase (ESBL) producers (Alsamawi *et al.*, 2022). A survey from Oman found *Escherichia coli* (32.39%), *Pseudomonas aeruginosa* (22.16%), *Klebsiella pneumoniae* (19.97%), and *Acinetobacter baumannii* (5.22%), with growing resistance against ciprofloxacin and meropenem (Sathya Kumar *et al.*, 2023). The factors included prolonged hospital stay, intravenous cannulation, multiple co-morbid conditions, and previous antibiotic exposure, which are attributed to the resistance in the present study. A study in Iran demonstrated that the most common gram-negative infections included *Klebsiella pneumoniae*, *Escherichia coli*, *Serratia marcescens*, and *Pseudomonas aeruginosa* (Mahmoudi *et al.*, 2023). The study also found

a high prevalence of carbapenem-resistant isolates, with more than 70% *Klebsiella pneumoniae* carbapenem-resistant; therefore, the implementation of antimicrobial stewardship and infection prevention measures is necessary to control the emergence and subsequent spread of AMR, as they are two facets of the same coin. In Sub-Saharan Africa, the levels of third-generation cephalosporins resistance in the bloodstream are reported to be high in *Escherichia coli* (18.4%), *Klebsiella sp.* (54.4%), non-typhoidal *Salmonellae* (1.9%) (Lester *et al.*, 2020). Studies from Finland, Australia, Sweden, and Canada have shown increased overall resistant *Escherichia coli* BSI rates (Buetti *et al.*, 2017). Persistent bacteremia was reported in 18 patients (5 %), with the most common pathogens being *Klebsiella sp.* and *Escherichia coli*. Source control was performed in only one-third of the patients; out of 30 patients, 13 (43.3%) have died due to persistent bacteremia; source control was performed for eight of them.

Persistent bacteremia is a serious condition that can lead to significant morbidity and mortality and increased healthcare costs (Iskandar *et al.*, 2021). The epidemiology of persistent GNB is complex and is influenced by factors such as prior antibiotic use, exposure to healthcare facilities, and comorbidities. Several studies have identified risk factors such as end-stage renal disease (ESRD) during hemodialysis, intravascular devices, bacteremia due to MDRO organisms, and ineffective antibiotic therapy as independent predictors of persistent GNB bacteremia (De Waele *et al.*, 2018). The incidence of persistent GNB is increasing, with higher rates observed in older adults and patients with comorbidities (De Waele *et al.*, 2018). Persistent GNBs are often seen in patients with weakened immune systems, such as malignancies, HIV, or organ transplants (Tumbarello *et al.*, 2012). The main contributing factors to GNB bacteremia were DM-2, hypertension, ischemic heart disease, and chronic kidney disease in the present study. Approximately 10% of patients had malignancy, and 6.7% were on immunosuppressive drugs.

The management of persistent bacteremia can be challenging and requires a multidisciplinary approach. The first step in management includes identifying the source of the infection. Appropriate antimicrobial therapy should be initiated with proper source control, including removing infected intravascular devices, such as central venous catheters, or surgical intervention to remove infected tissue. A reasonable approach for source control was observed in the patient population. Fortunately, there were only a handful of cases where it was indicated but not performed. Appropriate antibiotic therapy should be used based on the organism's susceptibility pattern to manage persistent GNB effectively. Chu *et al.* found that inappropriate initial antimicrobial treatment increases mortality risk (Chu *et al.*, 2020). All GNB bacteremia in patients are reported directly to the infectious disease physician on call by the Clinical Microbiology Department as a part of the antimicrobial stewardship

program. As part of the same stewardship, broad-spectrum antimicrobials are authorised by infectious disease physicians within 48 hours of initiation. A combination therapy may be necessary to achieve adequate bacterial clearance (Kalelkar *et al.*, 2022); the empirical antimicrobials were started according to study hospital guidelines and subsequently tailored to narrow-spectrum agents as soon as sensitivities were available.

Local epidemiology of infective organisms, antibiograms, immune status, previous antimicrobial exposure, possible source of infection, and colonisation with MDR bacteria and other alert microorganisms such as *Clostridium difficile* and *Candida auris* must be considered before initiating empirical therapy. Initial broad-spectrum antibiotics should be administered empirically in severely ill patients, followed by source identification and control as soon as possible (Timsit *et al.*, 2020). De-escalation from a broad-spectrum to a narrow-spectrum antimicrobial when culture and sensitivity results are available effectively reduces AMR (Lester *et al.*, 2020) and is rigorously followed in our hospital. On average, the duration of Intravenous (IV) antibiotics was 5-8 days, although longer durations were used when the underlying illness and source of infection were present. Another important intervention was the close teamwork relationship and clinical discussions between our infectious disease physicians and medical microbiologists in decision-making (De Waele *et al.*, 2018).

In South Korea, extended-spectrum beta-lactamase-producing Enterobacterales have emerged as a significant cause of community-acquired bacteremia after the prior use of antimicrobials (Timsit *et al.*, 2020). The present study did not look for previous use of antimicrobials but noted that last hospitalisation and prolonged hospital stay were associated with a higher emergence of resistance. Similarly, a study from Lebanon reported that infections caused by resistant bacteria were associated with a significant increase in hospital stays compared to those with susceptible bacteria, leading to higher costs (Iskandar *et al.*, 2021). The duration of antibiotic therapy for gram-negative bacteremia depends on several factors, such as the site of infection, severity of illness, and the type of causative organism. In this study, many patients received IV antibiotics for less than 7 days, while only 12% received treatment for more than 14 days (either due to persistent bacteremia or complicated bacteremia). Several studies have determined the optimal duration of antibiotic therapy for gram-negative bacteremia (Dyer *et al.*, 2019; Lee *et al.*, 2019). Yahav *et al.* found that a short course of antibiotic therapy (7 days) was as effective as a longer course (14 days) in the treatment of gram-negative bacteremia (Yahav *et al.*, 2019). A meta-analysis of three randomised controlled trials (RCTs) with 1121 patients with Enterobacterales bacteremia showed no significant difference in 90 days of mortality between 7 and 14 days of treatment (Turjeman *et al.*, 2023).

Shorter durations of antimicrobials are advocated as a goal for many antimicrobial stewardship programs

to treat community-acquired pneumonia, urinary tract infections, intra-abdominal infections, and skin and soft-tissue infections. Baltas *et al.* reported an overall mortality at 1 year of 36.2 %, with 18% within the first 30 days (Baltas *et al.*, 2021). Similarly, a study from Calgary found that 28-day, 90-day, and 365-day all-cause case-fatality rates after bloodstream infection were 12%, 17%, and 25%, respectively (Laupland *et al.*, 2011). A study by Qatar showed a hospital mortality rate of 29.7 % for all bacteremia cases (Khan *et al.*, 2010). A larger study examined the epidemiology of bloodstream infections in 51 countries across six continents in critically ill patients, including COVID-19 patients (Buetti *et al.*, 2017), found that gram-negative bacteria were the most common cause of bloodstream infections and the overall mortality for bloodstream infections was 45%, with higher rates reported in Covid-19 patients (Buetti *et al.*, 2017). Mortality due to gram-negative bacteremia can vary depending on various factors, such as the specific bacterial species involved, age and overall health of the patient, presence of underlying medical conditions, and promptness and effectiveness of treatment. The mortality from gram-negative bacteremia is higher than that from gram-positive bacteremia, with some studies suggesting mortality ranging between 20 and 50%. However, mortality rates can vary widely based on individual circumstances, and it is important to note that timely and appropriate antibiotic treatment can greatly improve outcomes in patients with gram-negative bacteremia. The incidence and mortality rates of gram-negative bacteremia can vary globally, depending on healthcare practices, antibiotic resistance patterns, and population demographics. The study centre has an antimicrobial stewardship program with formulary restriction and preauthorisation of restricted antimicrobials that aid in appropriately starting antimicrobials, particularly in bacteremia cases, and is followed by the infectious disease team in collaboration with the medical microbiologist, which could be one reason why the MDRO rate was not significantly high. However, cephalosporins are not restricted in clinical practice, which might explain the higher numbers of ESBL-producing Enterobacterales.

CONCLUSION

In conclusion, gram-negative BSIs are serious infections with increasing antimicrobial resistance (AMR). Extended-spectrum beta-lactamase (ESBL) producing bacteria are our centre's most common cause of AMR. Diabetes Mellitus-2, old age and hospital-acquired infections are risk factors leading to higher mortality. Healthcare professionals should be aware of the risk factors associated with this condition and initiate empirically effective antibiotic therapy to achieve optimal treatment outcomes and prevent collateral damage. Further research is needed to understand better the epidemiology and pathophysiology of gram-negative bacteremia in Qatar and formulate effective targeted treatment strategies.

LIMITATIONS

The limitations of our study include the need for more data on the prior use of antimicrobials and health care costs. The long-term impact of GNB beyond 3 months has yet to be investigated. The retrospective nature of this study and the single-center data are other limitations. Further analysis with a larger sample size is recommended to enhance the understanding of these findings in clinical practice. In this study, we only looked at long-term mortality within 90 days. Still, collateral damage was determined, such as the emergence of MDRO in 90 days at 6.1%, while infection with *Clostridioides difficile* occurred only in 2 patients (0.5%).

Acknowledgement

Clinical Microbiology Department and Pharmacy Department

Data Availability Statement

The data used to support the findings of this study were restricted by the Institutional Review Board (IRB) medical research centre at Hamad Medical Corporation to protect patients' privacy. Data can be obtained after IRB approval for researchers who meet the criteria for access to confidential data.

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