DOI: https://doi.org/10.54393/pbmj.v6i08.922

PAKISTAN BIOMEDICAL JOURNAL

https://www.pakistanbmj.com/journal/index.php/pbmj/index

Volume 6, Issue 8 (August 2023)

Original Article

Antimicrobial Drug Resistance Trends of Bacteria Causing Bloodstream Infections in a Diagnostic Centre in Lahore

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ARTICLE INFO

Key Words:

Bacteraemia, Multidrug Resistance, Staphylococcus epidermidis, Staphylococcus aureus, Salmonella typhi

How to Cite:

Minahil, S., Nazeer, K. ., Bashir, M. F. `, Asif, A., & Riaz, S. (2023). Antimicrobial Drug Resistance Trends of Bacteria Causing Bloodstream Infections in a Diagnostic Centre in Lahore: Antimicrobial Drug Resistance Trends of Bacteria. Pakistan BioMedical Journal, 6(08). https://doi.org/10.54393/pbmj.v6i08.922

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Received Date: 9th August, 2023
Acceptance Date: 29th August, 2023
Published Date: 31st August, 2023

ABSTRACT

Bacteraemia due to multidrug-resistant (MDR) bacteria, particularly those producing carbapenemase or extended-spectrum beta-lactamase (ESBL), causes a significant threat to patients and associated morbidity and mortality. The global rise in the incidence of bacteremia necessitates the rapid and accurate identification of pathogens to ensure effective patient health management. **Objective:** To investigate antimicrobial drug resistance trends among bacteria causing bloodstream infections from a diagnostic centre in Lahore. **Methods:** This research was conducted at the Institute of Microbiology and Molecular Genetics, University of the Punjab, Lahore and Citilab and Research Centre, Lahore, from January 2020 to December 2022. A total of 2919 blood samples were cultured to screen the bacteremia patients. Following standard protocols, four hundred twenty isolates proceeded for gram-staining, biochemical characterization, and antimicrobial susceptibility testing (AST). The AST results of each strain calculated multiple antibiotic resistance (MAR). **Results:** Of 420 bacterial isolates, Gram-negative and Gram-positive isolates accounted for 48.57% and 51.43%, respectively. The predominant pathogens were *Staphylococcus epidermidis* (48.10%) and *Salmonella typhi* (27.14%), with other significant pathogens including *Klebsiella* spp., *Pseudomonas* spp., *Enterobacter*, *Acinetobacter* spp., *Escherichia coli*, *Staphylococcus aureus*, *Enterococcus* spp., *Citrobacter*, *Morganella morganii*, and *Proteus mirabilis*. AST revealed high resistance to Cephalosporins, Nitrofurantoin, Fosfomycin, and Quinolones. In contrast, Carbapenems demonstrated notable sensitivity. *Salmonella typhi* and *Staphylococcus epidermidis* exhibit the highest MAR values. **Conclusions:** The study highlights the prevalence of multidrug resistance bacteremia-causing pathogens, with a concerning trend towards decreasing antibiotic efficacy.

INTRODUCTION

Bloodstream infections (BSIs) acquired in the community or healthcare settings substantially impact mortality and morbidity worldwide [1]. Numerous investigations have indicated that bloodstream infections ranked as the seventh leading cause of mortality. An estimated annual fatality rate of no less than 23 per 100,000 individuals follows shortly after experiencing a BSI episode. Hospitalised patients, particularly those immunocompromised, undergoing chemotherapy, equipped with intravascular catheters, or subjected to intensive antibiotic usage, are exceptionally susceptible to bacterial colonisation, localised infections, and even systemic infections [2]. Over time, the epidemiology of microbial pathogens responsible for BSI has evolved, showing a rise in the occurrence of both Gram-negative and Gram-positive organisms. Moreover, the emergence of antibiotic resistance has become a significant concern in the context of community-acquired bloodstream infections [3]. Bacteraemia can affect adults across all age groups, with its frequency gradually increasing after age 55 to 60 years [4]. Roughly 5-25% of young children experience fever due to severe bacterial infections like bacteraemia. In recent times, microorganisms like *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella*

DOI: https://doi.org/10.54393/pbmj.v6i08.922

pneumoniae, *Pseudomonas aeruginosa*, or *Salmonella* spp. have gained prominence in the context of community-acquired bacteraemia [3]. The existence of bacteria in the bloodstream, known as bacteraemia, presents an immediate concern for public health, capable of triggering severe illnesses and inflicting significant economic tolls on the global economy annually. Bacteraemia can lead to clinical sepsis, characterised by life-threatening organ dysfunction [5]. Diagnosis is accomplished by examining the patient's clinical symptoms and conducting laboratory tests [1]. Bacteraemia is linked to fever and chills but can also manifest without symptoms [5]. The clinical diagnosis of bacteraemia is confirmed through microbiological examination of blood samples. Blood cultures remain the definitive test for identifying individuals with bacteraemia. Isolating the microorganism from the bloodstream validates the diagnosis, enabling medical practitioners to pinpoint the infection's origin and subsequently prescribe suitable antimicrobial treatments [6]. The rise of antimicrobial resistance (AMR) in most bacterial pathogens presents a substantial global public health challenge. AMR remains an escalating concern within healthcare facilities, and it is linked to the rapid dissemination of multidrug resistant clones from hospital-acquired contexts to infections acquired within the community [7]. The "ESKAPE" pathogens can evade the bactericidal effects of antibiotics. This group includes E: *Enterococcus faecium*, S: *Staphylococcus aureus*, K: *Klebsiella pneumoniae*, A: *Acinetobacter baumannii*, P: *Pseudomonas aeruginosa*, and E: *Enterobacter* spp. These pathogens can acquire and propagate antibiotic resistance, contributing to over half of all infections associated with healthcare settings, and are closely linked to high rates of antimicrobial resistance. They pose a significant risk to patients, particularly those developing bloodstream infections, as limited treatment options and effective management strategies are available [7]. Bacterial infections with MDR have been linked to increased occurrences of complications, mortality, and recurrence. The constrained progress in creating new antibiotics has resulted in the challenging treatment of MDR infections [8]. The improper utilisation of antibiotics is associated with the emergence and dissemination of antibiotic-resistant bacteria. Interventions focusing on the prudent use of antimicrobials have been implemented to target antibiotic prescription practices within primary care environments [9]. By identifying the most prevalent drug-resistant pathogens and delineating the key drivers of resistance, the current study aims to evaluate the bacterial pathogens involved in BSIs and their antimicrobial susceptibility patterns in patients and to inform evidence-based interventions, guide antimicrobial stewardship efforts, and optimize therapeutic strategies for bacteraemia patients in Lahore.

METHODS

This study was based on an analysis of blood culture data to evaluate the rate of bacteria causing bloodstream infections. A total of 2919 patients visited the diagnostic Centre in Lahore, for blood culture tests. All data recorded on blood cultures submitted for detection of blood infection with antibiotic sensitivity testing (AST) was collected from the Microbiology Department of Citilab and Research Centre, Lahore. Demographic information of patients of blood sample were obtained. All samples were taken in blood culture bottles containing Tryptic Soy Broth with SPS and incubated at 37°C overnight. Culture broth with positive signs of bacterial growth was streaked on Blood agar, Chocolate agar and MacConkey's agar plates and incubated for 24-48 hours at 37°C. The purified colonies were selected to identify based on colony morphology and gram staining. According to the microbiological manual, the biochemical characterization was carried out by multiple tests, including triple sugar iron, citrate utilization, methyl red, oxidase, motility, Voges Proskauer, and indole. Antibiotic susceptibility testing of strains was performed on Muller Hinton agar (MHA) using Kirby Bauer's method. Around 30 antibiotic discs were tested for antimicrobial activity against the organisms under study. The plates were prepared by pouring MHA to a depth of 3 mm and then swabbing them with the test organisms. The paper discs were placed on the surface of agar plates aseptically and at well-spaced intervals of >30mm. For gram negative isolates, antibiotics discs applied were; AM (10 µg), AMC (30 µg), AZM (15 µg), CRO (30 µg), CE (30 µg), CIP (5 µg), C (30 µg), CN (10 µg), DA (2 µg), E (15 µg), FOX (30 µg), F (300 µg), FF (50 µg), FA (10 µg), LEV (5 µg), LZD (30 µg), MXF (5 µg), NOR (10 µg), OX (1 µg), P (10 U), SXT (25 µg), TE (30 µg), TEC (30 µg), VA (30 µg). For gram positive isolates, antibiotics discs applied were; AK (30 µg), AM (10 µg), AMC (30 µg), ATM (30 µg), AZM (15 µg), CAZ (30 µg), CEZ (30 µg), CFM (5 µg), CEP (75 µg), CXM (30 µg), CRO (30 µg), CE (30 µg), CIP (5 µg), CES (75/30 µg), C (30 µg), CT (10 µg), CN (10 µg), FEP (30 µg), FF (50 µg), IPM (10 µg), MEM (10 µg), LEV (5 µg), NA (30 µg), SXT (25 µg), TOB (10 µg), TE (30 µg), TPZ (110 µg). After incubation, the plates were observed for the zone of inhibition around the disc. For 18 hours, the bacterial test plates were incubated at 37°C. Finally, the inhibition zone diameters were measured in millimeters. A relative antibiotic resistance profile among different clinical pathogens is determined using the Multiple Antibiotic Resistance Index. The MAR index of any isolate is calculated as a ratio of 'a' to 'b', where 'a' is the number of antibiotics for which resistance has been determined, and 'b' is the number of antibiotics used on each isolate. For each isolate, the MAR Index was calculated.

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RESULTS

A total of 420 (14.38%) bacteria were isolated from 2919 blood cultures received in the Microbiology section of the Lab. The most affected age group was 1-20 years. 120 (40.13%), followed by 21-40 years 93 (31.10%), 41-60 years 45 (15.05%) >1 year 23 (7.69%) and 61-80 years 17 (5.68%). Blood infections were more predominant in females 180 (53.0%) than in males 159 (46%) (Table 1).

Table 1: Profile of common bacterial species isolated from blood cultures with corresponding demographical distribution

Organisms	Age (years)						Sex		Total n (%)
	<1 yr. n (%)	01-20 yrs. n (%)	21-40 yrs. n (%)	41-60 yrs. n (%)	61-80 yrs. n (%)	>80 yrs. n (%)	Male n (%)	Female n (%)	
Acinetobacter	3 (33.3)	2 (22.2)	2(22.2)	0	2(22.2)	0	4 (44.4)	5(55.6)	9 (2.14)
Citrobacter	2 (33.3)	1(16.7)	1(16.7)	1(16.7)	1(16.7)	0	2(33.3)	4(66.7)	7 (1.67)
Enterobacter	2 (18.2)	4 (36.4)	4 (36.4)	1(9.1)	0	0	6 (50)	6(50)	14 (3.3)
Escherichia coli	2 (22.2)	2 (22.2)	1(11.1)	3(33.3)	1(11.1)	0	5 (55.6)	4(44.4)	9 (2.14)
Klebsiella spp.	2 (16.7)	2 (16.7)	7 (58.3)	1(8.3)	0	0	5(31.3)	11(68.7)	17 (4.05)
Morganella morganii	0	0	1 (100)	0	0	0	1(100)	0	1 (0.24)
Proteus mirabilis	0	0	1 (100)	0	0	0	1(100)	0	1 (0.24)
Pseudomonas aeruginosa	0	1 (100)	0	0	0	0	0	3 (100)	9 (2.14)
Pseudomonas spp.	0	5 (50)	2 (20)	2 (20)	1 (10)	0	6 (54.5)	5 (45.5)	16 (3.81)
Salmonella typhi	3 (3.2)	72 (75)	18 (18.7)	3 (3.13)	0	0	61 (58.6)	43 (41.4)	114 (27.2)
Salmonella paratyphi	0	4 (57.1)	3 (42.8)	0	0	0	4 (57.2)	3 (42.8)	7 (1.67)
Staphylococcus epidermidis	8 (6.4)	23 (18.4)	50 (40)	32 (25.6)	11 (8.8)	1 (0.8)	60 (40.5)	88 (59.5)	202 (48.1)
Staphylococcus aureus	0	2 (28.7)	2 (28.6)	2 (28.6)	1 (14.3)	0	1 (12.5)	7 (87.5)	9 (2.14)
Enterococcus	1 (25)	2 (50)	1 (25)	0	0	0	3 (75)	1 (25)	5 (1.19)
Total	23	120	93	45	17	1	159	180	

Of 420 isolates, 176 (41.90%) were found to be non-lactose fermenters and 28 (6.66%) lactose fermenters on MacConkey agar. Biochemical characterization of each blood isolate revealed the frequency of Gram-negative isolates was 204 (48.57%) and Gram-positive 216 (51.43%). Among gram-negative isolates, *Salmonella typhi* most frequently identified strain 114 (55.88%), then *Klebsiella* spp. 17 (8.33%). The prevalence of other strains, including *Pseudomonas* spp., was 16 (7.84%) and *Enterobacter* 14 (6.86%). *P. aeruginosa*, *Acinetobacter* spp. and *E. coli* were the same in number as 9 (4.41%) and *Citrobacter* and *S. paratyphi* were 7 (3.43%). *M. morganii* and *P. mirabilis* 1 (0.49%) were isolated from the single patient sample with the least frequency *S. epidermidis* was the most predominant gram-positive isolate 216 (51.43%). 202 (93.51%). They were followed by *S. aureus* 9 (4.16%) and *Enterococcus* spp. 5 (2.31%) (Figure 1).

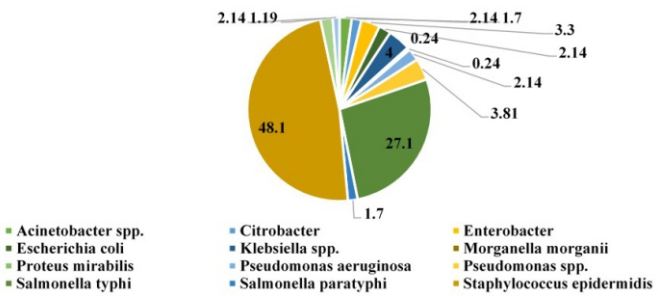

Figure 1: Number of bacterial isolates from blood of bacteremia suspected patients

In Gram-negative bacteria, antibiotics belonging to Cephalosporins, Nitrofurantoin, and Fosfomycin exhibited high resistance. CEZ, CE, F, FF were 100% resistant. Other antibiotics showing resistance: CAZ 95.5%, NA 93.4%, AM 88.8%, SXT 86.0%, AMC 84.6%, CXM 77.6%, C 69.7%, CRO 68.7%, CEP 68.2%, FEP 67.2%, CFM 63.0%, ATM 61.8%, AZM 53.8%, CES 44.8%, TOB 44.6%, CIP 42.2%, CN 39.8%, TPZ 33.2%, LEV 31.4%, AK 25.3%, TE 24.2%, CT 18.2%, and IPM, MEM both with 7.5%. Carbapenems revealed the highest sensitivity as IPM and MEM, 92.0%. Other antibiotics that showed high sensitivity include CT 81.8%, TE 75.3% and AK 73.5%. In Gram-positive bacteria, antibiotics belonging to Cephalosporins, Nitrofurantoin, Fosfomycin and Quinolones were highly resistant. CRO, F, FF, LEV, and NOR exhibited 100% resistance. Other antibiotics showing resistance: SXT 94.8%, AZM 77.5%, P 75%, AMC 71.8%, E 69.5%, FOX 66.7%, OX 66.7%, CIP 64.5%, TE 61.3%, AM 60%, MXF 53.1%, FA 43.3%, CN 20.4%, DA 17.1%, C 8.3%, LZD 3.7%, VA 0.5%, CE and TEC both with 0%. Cephalosporins and Glycopeptide antibiotics revealed the highest sensitivity as CE and TEC 100%. Other antibiotics that showed high sensitivity include VA 99.5%, LZD 96.3%, and C 91.7%. DA 82.4% and CN 79.6%. Among the antibiotics used for susceptibility testing (AST), Ampicillin 151 (88.8%) showed the highest activity against *Enterobacteriaceae*, Cefepime 24 (70.69%) against non-*enterobacteriaceae* and Sulphamethoxazole 200 (92.6%) against Gram-positive cocci. Then, Sulphamethoxazole 146 (85.9%), Ceftazidime

DOI: https://doi.org/10.54393/pbmj.v6i08.922

21 (61.8%), Azithromycin and Penicillin 162 (75%) were resistant against *Enterobacteriaceae*, *non-enterobacteriaceae* and Gram-positive cocci, respectively.

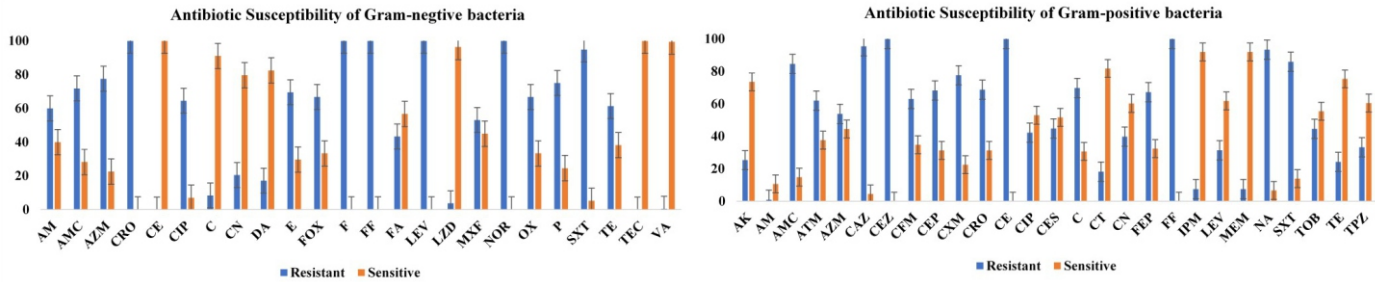

Figure 2: Rates of resistance of gram-negative and positive bacteria to different testing antibiotics

The trend of antimicrobial resistance was apparent for each strain (Table 2). Among the Gram-negative bacteria, the most common pathogen of *S. typhi* had MAR values in the range of 0.71-0.8 24.56%, then 0.61-0.7 22.81%, 0.21-0.3 10.53%, 0.51-0.6 8.77%, 0.81-0.9 7.89%, 0.11-0.2 7.02%, 0.01-0.1 6.14% and 0.31-0.4% 6.14%, 0.41-0.5 4.38%, 0 0.88%, 0.91-1 0.88%. The resistance pattern for *S. epidermidis* was 0.51-0.6 29.70%, 0.31-0.4 22.28%, 0.41-0.5 14.85%, 0.11-0.2 10.39%, 0.61-0.7 8.91%, 0.21-0.3 5.94%, 0.71-0.8 3.47%, 0.01-0.1 2.97%, 0 1.49%.

Table 2: MAR range of different bacteria isolated from blood

Clinical Isolates	MAR Range					
	Total strains	0.0-0.2 n (%)	0.21-0.4 n (%)	0.41-0.6 n (%)	0.61-0.8 n (%)	0.81-1.00 n (%)
Gram-negative bacterial isolates						
Salmonella typhi	114	16 (14)	19 (17)	15 (13)	54 (47)	10 (9)
Klebsiella spp.	17	5 (29)	2 (12)	6 (35)	3 (18)	1 (6)
Pseudomonas spp.	16	4 (25)	2 (13)	6 (38)	4 (25)	0 (0)
Enterobacter	14	1 (7)	0 (0)	3 (21)	4 (29)	6 (43)
Pseudomonas aeruginosa	9	5 (56)	2 (22)	1 (11)	0 (0)	1 (11)
Acinetobacter spp.	9	2 (29)	0 (0)	0 (0)	2 (22)	5 (56)
Escherichia coli	9	0 (0)	2 (22)	1 (11)	5 (56)	1 (11)
Citrobacter	7	1 (14)	2 (29)	0 (0)	2 (29)	2 (29)
Salmonella paratyphi	7	3 (43)	2 (29)	0 (0)	2 (29)	0 (0)
Morganella morganii	1	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)
Proteus mirabilis	1	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Gram-negative bacterial isolates						
Staphylococcus epidermidis	202	30 (15)	57 (28)	90 (45)	25 (12)	0 (0)
Staphylococcus aureus	9	2 (22)	0 (0)	7 (78)	0 (0)	0 (0)
Enterococcus spp.	5	2 (40)	1 (20)	2 (40)	0 (0)	0 (0)

DISCUSSION

In this study, 420 (14.38%) bacteria were isolated from a blood sample of patients. Encouraging our results, a study on hematologic malignancies found nearly the same percentages of bloodstream infections, 13.4% [10]. Rates of blood infections are mostly observed in ranges between 11% to 38%, with overall mortality reaching 40% [11]. The proportion of gram-positive isolates 216 (51.43%) was higher than gram-negative isolates 204 (48.57%). Similar to our findings, around 60% of primary bloodstream infections were attributed to gram-positive cocci that can enter the bloodstream via different procedures [12]. Whereas Droz *et al.*, reported 63.9% gram-negative and 35.8%-gram-positive isolates in a meta-analysis [13]. Bacteremia was more common in women than men, with 52.8% and 47.2%, respectively. In contrast to our results, male was more likely to be affected in a retrospective study [14]. A recent study in Pakistan found the roughly same male/female ratio, accounting for 55.5% and females 44.5%, respectively [15]. Another study by Morelli *et al.*, on maternal sepsis found that bacteraemia accounted for 15% maternal deaths and 5% of admissions in the intensive care unit (ICU). This was due to the high exposure of women to healthcare systems. The use of antibiotic injections during pregnancy leads to complications [16]. In our study, *S. epidermidis* was predominant among gram-positive isolates and *S. aureus*. *S. epidermidis* as a commensal organism living on human skin membranes and able to survive on medical devices by biofilm production. However, its entry into blood through medical devices makes it a nosocomial bacteraemia pathogen [17]. *Staphylococcus epidermidis* is one of the primary causes of nosocomial bloodstream infections. Individuals with prosthetic valves, cardiac devices, central lines, catheters, and intravenous

DOI: https://doi.org/10.54393/pbmj.v6i08.922

drug use face heightened susceptibility to these infections [18]. In other countries like Canada and the USA, *S. aureus* is mainly associated with high bacteraemia rates [19]. The second most common pathogen in our study was *S. typhi. Salmonella typhi* was the most common cause of sepsis among gram-negative isolates [13]. Typhoid fever has been a serious global health concern, especially in the last five years. Pakistan has faced outbreaks of ST from 2016 to 2019 [14]. The literature revealed the fact that typhoidal XDR-ST cases are continuously increasing in Pakistan. Other bacteraemia-causing pathogens were *Klebsiella* spp. *Pseudomonas* spp. *Enterobacter*, *P. aeruginosa*, *Acinetobacter* spp. and *E. coli*, *Citrobacter* and *S. paratyphi*, *M. morganii* and *P. mirabilis* and *Enterococcus* spp. All these bacteria were included in the group "ESKAPE," which are the most common multidrug-resistant pathogens according to the Centers for Disease Control and Prevention (CDC) and the European Centre for Disease Prevention and Control (ECDC) [15]. *A. baumannii* is one of these six most important multidrug-resistant bacteria associated with 8.4% cases of bacteraemia in Lahore [20]. AST results have shown the highest percentage of resistance in gram-negative and gram-positive isolates for cephalosporins, ciprofloxacin, and trimethoprim/sulphamethoxazole antibiotics. Carbapenems revealed the highest sensitivity in gram-negative bacteria. Multiple antibiotic resistance index revealed a large % of isolates 82.86% with a MAR index greater than 0.2, and 17.14% of isolates were equal to or less than 0.2. According to a study, the MAR index indicated that 76.34% of isolates had a MAR index above 0.2, while 23.66% had a MAR below 0.2 [21]. The most common gram-negative isolate *S. typhi,* had the highest MAR values in the range of 0.71-0.8, i.e., 24.56%. And the predominant strain of gram-positive infections *S. epidermidis* had the highest resistance pattern in the range 0.51-0.6, i.e., 29.70%. A previous study in Pakistan revealed the pooled prevalence of ESBLs producing bacteria was 40% [22]. Another study highlighted the rapid increase in carbapenem resistance rates to antibiotics in *Acinetobacter* species and a noticeable rise in third and fourth-generation cephalosporins resistance in *Salmonella typhi* in the last five years. Whereas *S. aureus* with decreasing resistance trends was observed between 2011–2015. Two studies in Pakistan reported the emergence of MDR isolates in *Salmonella typhi* and XDR was 76% (182 isolates) and 48% (115 isolates) during previous outbreaks [23, 24]. Extensive use of beta-lactam drugs, aminoglycosides and other antibiotics is one of the major factors that lead to the emergence of extended-spectrum beta-lactamase *Enterobacteriaceae* (ESBL), carbapenem-resistant *Enterobacteriaceae* (CRE), gentamicin-resistant Gram-negatives, methicillin-resistant *S. aureus* (MRSA), and vancomycin-resistant enterococci (VRE) [25]. Moreover, AMR trends differ from country to country due to different antimicrobial usage, healthcare facilities and policies for infection management [26]. Nowadays, the antibiotic use rate in Pakistan is higher than in other Asian countries [7]. These elevated levels of consumption of antibiotics are the major reason behind AMR rise [27]. Regular updating protocols to use antibiotics and antimicrobial resistance profiles of prevalent bacteria are essential to control drug-resistant bacteraemia.

CONCLUSIONS

Bacteraemia mainly occurs in females. The infected individuals were mostly between 1-20 and 21-40 years old. The leading gram-positive and gram-negative bacteria were *Staphylococcus epidermidis* and *Salmonella typhi*. Antibiotic susceptibility tests showed 100% resistant antibiotics, including cephalosporins, nitrofurantoin, fosfomycin, and quinolones. Carbapenems were among the most sensitive antibiotics. Ampicillin, cefepime and sulphamethoxazole had the highest antimicrobial activity. *S. typhi* had the highest MAR value in the range 0.71-0.8 and *S. epidermidis* in the range 0.51-0.6. Pathogens are becoming resistant to previously used antibiotics, and the trend is shifting towards multidrug resistance.

Authors Contribution

Conceptualization: SM, KN
Methodology: MFB
Formal Analysis: AA
Writing-review and editing: SM, KN, MFB, AA, SR

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship and/or publication of this article.

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