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Research Article

Multi-Drug Resistance Profile of Bacteria Isolated from Blood Stream Infection at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia

Seneshat Eshetu[1], Adane Bitew[2]*, Tigist Getachew[2], Dessie Abera[2] and Solomoan Gizaw[3]

[1]Department of Medical Laboratory, Amanuel Mental Specialized Hospital, Addis Ababa, Ethiopia

[2]Department of Medical Laboratory Sciences, College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia

[3]Department of Medical Laboratory, Tikur Anbessa Specialized Hospital, Collage of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia

***Corresponding Author**: Adane Bitew, Department of Medical Laboratory Sciences, College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia.

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Abstract

Background: Hospital acquired bloodstream infections are major cause of mortality and morbidity.

Objective: To assess bacteria implicated in causing blood stream infections and their multidrug resistance profile.

Method: A single institutional cross-sectional study was conducted at Tikur Anbessa Specialized Hospital from September 1/2016 to October 30/2017. A total of 422 blood samples were collected and cultured on blood agar bottles and bacteria were isolated and characterized by conventional methods. Antibiotic susceptibility testing was carried by Kirby Bauer disc diffusion technique.

Results: Out of a total of 422 samples processed, bacterial pathogens were isolated from 64 (15.2%) samples. Among the isolates, 29 were Gram- positive and 35 were Gram negative bacteria. *Staphylococcus aureus* and *Klebsiella pneumoniae* were the dominant isolates. Penicillin (86.7%) was the least effective antibiotic against Gram-positive bacteria while ampicillin (85.7%) and amoxicillin clavulanic acid (77.14%) were the least effective antibiotic against Gram-negative bacteria. Clindamycin (80%) and amikacin (97.1%) were the most effective antibiotic against Gram positive and Gram-negative bacteria, respectively. Out of 29 isolate of Gram-positive bacteria, 16 (55.2%) were multidrug resistant of which 11 (35.9.3%) were extensively drug resistant and 2 (6.9%) were pandrug resistant. Out of 35 isolates of Gram- negative bacteria, 26 (74.3%) were multidrug resistant of which 18 (54.4%) were extensively drug resistant.

Conclusions: The magnitude of blood stream bacterial infection and the prevalence rate of multi-drug resistant bacterial strains causing blood stream infections were high. These findings warranted the need for continuous investigations of bacteria implicated in causing blood stream infection and evaluation of their antibiotic susceptibility profile in health institution large scale.

Keywords: *Bacterial Blood Stream Infection; Multidrug Resistant; Nosocomial Infections; Extensively Drug Resistant; Pandrug Resistant Ethiopia; Addis Ababa*

Aberrations

MDR: Multidrug-Resistant; XDR: Extensively Drug Resistant; PDR: Pandrug Resistant; CONS: Coagulase Negative *Staphylococci*; BSI: Blood Stream Infection

Introduction

Blood stream infections are among the most common nosocomial infections causing significant mortality and morbidity worldwide [1-5]. Blood stream infections account for 10 - 20% of all hospital acquired infections and rank 8th in causing mortality [6]. Globally, 31.5 million cases of bacteremia occur annually and 5.3 million people have died with mortality rates ranging from 20 - 50% [7-10]. In sub-Saharan countries, including Ethiopia BSIs mostly occurs in children under 5 years age. The mortality rate of children in developing countries versus the developed countries is reported to be in the range of 100 - 250 and 10 - 30 per 1,000, respectively [11].

Hospitalization, non-adherence to infection control practices of health professionals, and implantation of foreign bodies such as catheters into blood vessels and other predisposing factors like intensive care unit have been incriminated as a major risk factors [11,12].

Acinetobacter species, *Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae* coagulase negative *staphylococci* (CoNS), *Staphylococcus aureus, enterococci,* and alpha-hemolytic *streptococci* have been reported as a predominant Gram-positive and Gram-negative bacteria implicated in causing blood stream infection [13-15].

Even though a number of studies [8,16,17] regarding the spectrum of bacteria associated with BSIs and their antibiotic resistance pattern have been conducted in Ethiopia, none of these studies addressed the magnitude of multidrug resistance profile of bacteria. Antibiotic resistance has recently been identified as one of the three most important problems facing human health by the World Health Organization [18]. Frequent isolation of multi-drug-resistant pathogens in both nosocomial and community-acquired infections further intensified the problem of antibiotic resistance [19]. *A. baumanni*i and *P. aeruginosa* with *E. faecium, S. aureus, K. pneumoniae,* and *Enterobacter* spp have been recognized as the most common and serious multi-drug -resistant pathogens [20]. Against this back ground, the aim of this study was to isolate and determine multi-drug resistance pattern of bacteria isolated from patient blood' admitted to Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia.

Materials and Methods

Study design and population

A single institutional cross-sectional study was conducted at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia from September 1/2016 to October 30/2017. Prior to sample collection, patients suspected of blood stream infection were clinically investigated by physicians on duty and signs and symptoms of blood stream infection were recorded. Patients diagnosed as having blood stream infections clinically, willingness to participate in the study, and no history of antibiotic treatment within the last 72 hours before sample collection were the inclusion criteria. Socio-demographic information of participants was taken from laboratory requisition form. Age groups of patients were classified following WHO guidelines [21].

Sample collection, blood culture and bacterial identification

Prior to blood collection, the skin of each study participant was disinfected with 70% alcohol and subsequently with Povidone-iodine. About 10 ml and 5 ml of venous blood in duplicates were collected aseptically from adults and children, respectively. Blood collected from each patient was inoculated into two blood culture bottles containing 50 ml and 25 ml of sterile brain heart infusion broth (Oxoid, Basingstoke, UK) aseptically. All blood culture broths were then incubated at 37^0C; checked for sign of bacterial growth daily up to 7 days. Blood culture bottles that showed signs of growth were sub-cultured onto Blood agar base (Oxoid, Basingstoke, UK)) to which 10% sheep blood is added, Chocholate agar (Oxoid, Basingstoke, UK)) and, MacConkey agar (Oxoid, Basingstoke, UK)) in safety cabinet. Blood culture broth with no bacterial growth after 7 days were sub-cultured before being reported as a negative. Pure isolates of bacterial pathogen were preliminary characterized by colony morphology and Gram-stain. In the case of mixed culture only significant bacterium was used for further study. Preparation and performance evaluation of culture media were done as per the instruction of the manufacturer.

Antibiotic susceptibility testing

The antibiotic susceptibility testing was performed according to Kirby-Bauer disk diffusion method on Mueller Hinton agar plates (Oxoid, Basingstoke, UK) [22]. The following antibiotics with their concentrations were used in our study. Ampicillin (10 µg), Amoxicillin/clavulanic Acid (10 µg), Penicillin (10 µg), Gentamicin (10 µg), Tobramycin (10 µg), Erythromycin (15 µg), Clindamycin (2 µg), Trimethoprim sulphamethoxazole (1.25/23.75 µg), Vancomycin (30 µg) Ceftriaxone (30 µg), Cefoxitin (30 µg), cefotaxime (30 µg), Ciprofloxacin (5 µg), Ceftazidime (30 µg), Amikacin (30 µg) and Meropenem (10 µg) All antibacterial drugs used in this study were the products of Oxoid, Basingstoke, UK.

The minimum inhibitory concentration were interpreted according to the Clinical Laboratory Standards Institute [22] after an incubation period of 24 hours at 350C aerobically and/or in a carbon dioxide incubator.

Quality control

The following standard reference strains of *S. aureus* (ATCC 25923), *E. coli* (ATCC 25922) and *P. aeruginosa* (ATCC 27853) were used as control organisms to check the quality of the antibacterial agents.

Definitions

No agreement has yet been reached on the definition and use of terms such as 'multidrug-resistant' extensively drug-resistant and 'pandrug-resistant', which characterize resistance. As per standardized international terminology created by European Centre for Disease Control (ECDC) and Centre for Disease Control and Prevention (CDC), Atlanta, the multidrug-resistant (MDR), extensively drug-resistant (XDR), and pandrug-resistant (PDR) bacteria have been well defined [23]. Multidrug resistant (MDR) was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories. Extensively drug resistant (XDR) was defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories. Pandrug resistant (PDR) was defined as non-susceptibility to all agents in all antimicrobial categories. The above definitions were used in the present work.

Ethical clearance

The study was approved by the Department of Research and Ethical Review Committee (DRERC) of the Department of Medical Laboratory Science, Collage of Health Sciences, Addis Ababa University. Informed consent was obtained from the parents or legal guardians. In addition, assent was taken from children under the age of 18 before data collection. The participants were informed their right to withdraw at any time during study period. Participants who were positive for bacterial pathogen were linked to the hospital clinicians and received proper treatment.

Result and Discussion

As shown in table 1, female patients were more affected (36; 54.5%) than male patients (30; 45.5%). Similarly, the infection rate was higher (64.2%) in study subjects less 15 years of age than the other age categories. Our finding was consistent with similar local study [24].

Variables	Category	Samples collected N = 422	Samples collected n = 422	
			BIs no = 358	BIs yes = 64
Age	< 1 years	61 (14.5%)	50 (13.9%)	11 (17.2%)
	1 - 14 years	191 (45.3%)	160 (44.9%)	31 (47.0%)
	15 - 24 years	64 (15.2%)	58 (16.2%)	6 (9.3%)
	25 - 44 years	71 (16.8%)	57 (16.0%)	14 (21.2%)
	45 - 64 years	23 (5.5%)	21 (5.9%)	2 (3.0%)
	> 65 years	12 (2.8%)	12 (3.4%)	0 (0.0%)
Gender	Female	186 (44.1)	150 (42.1%)	36 (54.5%)
	Male	236 (55.9)	206 (57.9%)	30 (45.5%)
Total		422 (100)	358 (84.8%)	64 (15.16%)

Table 1: *Demographic characteristics of study participants.*

Culture positivity rate varies from one study to another. Culture positivity rate of 64/422 (15.2%) in the current study was comparable with the culture positivity rates recorded in Jimma 15.8% [9], Zanzibar 14% [25], Pakistan 16% [26], Nigeria 13.1% [27], and Dhaka 14.38% [28]. However, the culture positivity rate obtained in the present study was higher than studies conducted in Jimma 8.8% [16], Nepal 7.3% [29], India (8.3%, 9.3%) [11,30] and Tanzania 5.6% [31]. It was lower than the culture positivity rate documented in Mekelle 28% [32], Gonder 18.2% [8], India 22.3% [12], Nigeria 19.3% [27], Turkey 21.3% [33], and Lebanon 18.6% [34]. Difference in study design, number of study population, blood culture system, geographical location, and epidemiological difference of the etiological agents, seasonal variations, in infection control policies between nations may be possible explanations.

As depicted in figure 1, a total of 64 bacterial isolates were recorded of which 29/64 (45.3%) and 35/64 (54.7%) were Gram-positive and Gram-negative bacteria, respectively. This finding was in agreement with previous studies carried out in Addis Ababa and Afghanistan [35,36], but in in contradiction with the findings of studies conducted in Gonder, Jimma, and Mekelle [8,9,32] in which Gram-positive bacteria outnumbered those of Gram-negative bacteria. The predominant bacterial isolate were *S. aureus* (23.4%) followed by *K. pneumoniae* (17.2%) and the least were *S. pneumoniae, Citrobacter* spp, and *Serratia marcescens* each accounting for 1.6% (Figure 1). Among Gram-positive bacterial isolates, *S. aureus* was the major isolate accounting for 23.4% which is in good agreement with studies conducted in USA 22.8%, Cameron 20.9%, and Addis Ababa 21.1% [2,10,37]. However, it was not in line with the results of studies carried out in Jimma 40%, Mekelle 37.5%, India 47.7%, and Nepal 65% [9,32,38,39]. As opposed to earlier reports [5,6 8,16], the isolation rate of CoNS in the present study was low. This might be due to the fact that, in the present study CoNS were considered as pathogen if they were isolated from duplicate blood culture bottles rather than from only one blood culture bottle. In most studies CoNS were considered as contaminants, in spite of the fact that they have become the major cause of nosocomial bloodstream infections. Increased use of artificial intravascular medical devices and admission of increased number of immune-compromised patients have been identified as possible explanations [10].

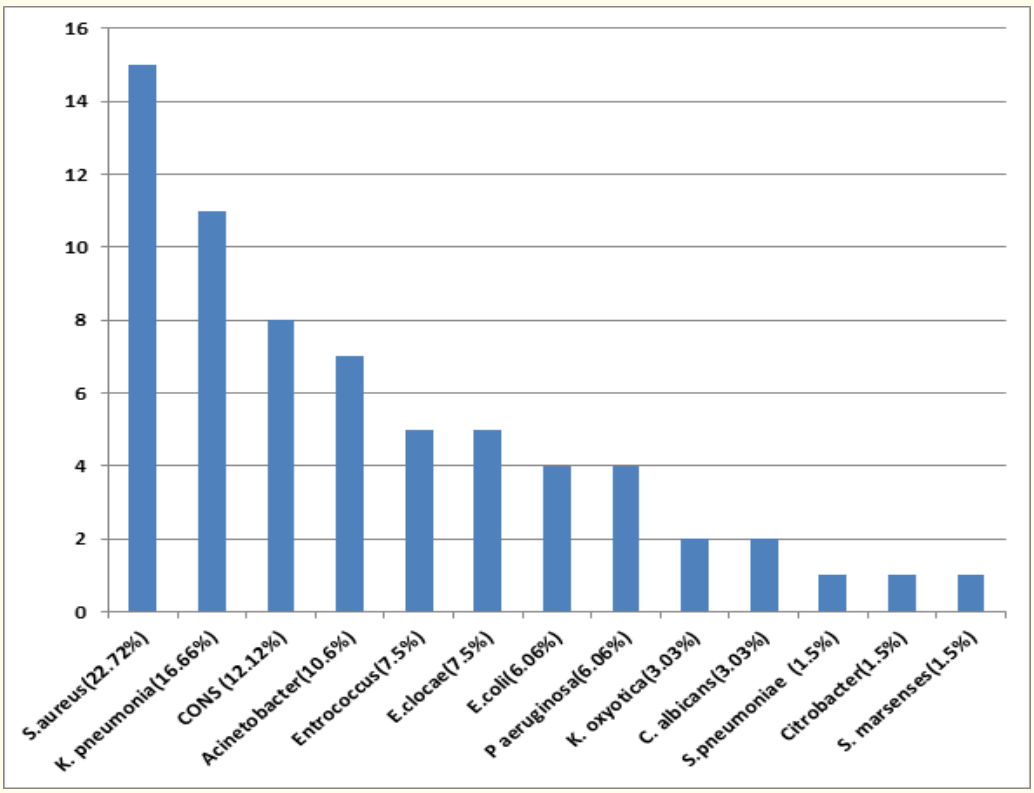

Figure 1: *Frequency and types of bacterial isolates from blood cultures.*

Klebsiella pneumoniae was the predominant (17.27%) isolate among Gram-negative bacteria. *K. pneumoniae* as a predominant Gram-negative bacterium in blood stream infection was reported in studies conducted in Nigeria 22% [27], Afghanistan 16.1% [36], South Africa 12.1% [40] and Iran 33.5% [3]. This was followed by *Acinetobacter* spp., *E. cloacae, E. coli*, and *P. aeruginosa.* Non-fermenting Gram negative bacilli such as *Acinetobacter* spp and *P. aeruginosa* have emerged as a major cause of healthcare-associated infections, especially in immune-compromised hosts [41].

The antibiotics tested and percentage antibiotic susceptibility profile of Gram-positive and Gram-negative bacteria are shown in table 2 and 3 respectively. The overall resistance rates of Gram-positive bacteria ranged from 25% for both gentamycin and clindamycin to 87.5% for penicillin. The overall antibiotic resistance rates of 23.5 - 58.8% [8], 0 - 100% [9] and 0 - 85.7% [16] in local studies and 14.3 - 87.5% in international study [27] have been reported. About eight seven percent of strains of S. aureus, the most commonly isolated Gram- positive bacterium, was resistant to penicillin and ampicillin. Our result was comparable with the results of researches conducted, in Iran, Nigeria, Jimma, and Afghanistan [3,27,16,36]. In the present study, among *S. aureus* isolates, 40.0% were methicillin resistant (cefoxitin). More or less similar observations were seen in other studies done in, India (33.3%), Turkey 60%, Afghanistan 51%, and [11,30,36]. Very high resistance rates of *S. aureus* against the beta lactam antibiotic (penicillin) and ampicillin could be the result of production of beta lactam enzymes.

Bacterial isolates	Bacterial isolates resistant to each drug tested (%)								
	CRO	CXT	VA	CN	E	DA	SXT	P	AMP
S. aureus (n = 15)	46.7	40.0	NT	40.0	26.7	20.0	33.34	86.7	86.7
CONS (n = 8)	75	50.0	NT	0	37.5	37.5	62.5	100	100
Enterococcus (n = 5)	NT	NT	60.0	NT	NT	NT	NT	NT	80.0
S. pneumoniae (n = 1)	0	NT	NT	NT	0	0	100	0	0
Total (29)	54.2	43.47	60.0	25.0	29.1	25.0	45.80	87.5	86.2

Table 2: *Percentage antibiotic resistance pattern of Gram- positive bacterial isolates from blood culture. CRO: Ceftriaxone; CXT: Cefoxitin; VA: Vancomycin; CN: Gentamicin; E: Erythromycin, DA: Clindamycin; SXT: Trimethoprim-Sulphamethoxazole; P: Penicillin; AMP: Ampicillin, NT: Not tested*

Bacterial isolates	Bacterial isolates resistant to each drug tested (%)									
	CTX	AMP	AMC	CRO	AK	MEP	CAZ	CIP3	CN7	TOB
K. pneumoniae (n = 11)	81.8	100	90.9	81.8	0	0	72.7	27.3	63.6	54.5
Enterobacter cloacae (n = 5)	80.0	100.0	60.0	80.0	20.0	0	40.0	20.0	60.0	20.0
E. coli (n = 4)	50.0	75	100	50.0	0	0	25	25.0	0	25.0
K. oxyotica (n = 2)	50.0	100	100	50.0	0	0	100	100	0	50.0
Citrobacter (n = 1)	100	100	100	100	0	0	100	0	0	0
Serratia (n = 1)	100	100	0	100	0	0	100	0	100	0
P. aeruginosa (n = 4)	NT	75	50	NT	0	25	50	25	25	50
Acinetobacter (n = 7)	NT	71.4	85.7	NT	0	28.6	71.4	42.9	42.9	42.9
Total (35)	75.0.	88.6	80.0	75.0	2.85	8.5	62.8	31.4	42.8	40.0

Table 3: *Percentage antibiotic resistance pattern of Gram- negative bacterial isolates from blood culture. CRO: Ceftriaxone: CN7: Gentamicin; AMP: Ampicillin, CTX: Cefotaxime; AMC: Amoxicillin-Clavulanic acid; AK: Amikacin; MEP: Meropenem; CIP: Ciprofloxacin; TOB: Tobramycin; CAZ: Ceftazidime; NT: Not tested*

Percentage over all resistance rates of Gram-negative bacteria ranged from 2.9% for amikacin to 80% and 86% for amoxicillin/clavulanic acid inhibitor combination and ampicillin, respectively. Percentage overall resistance rates of Gram-negative bacteria of 20 - 100% [8], 14.3 - 85.7% [9], 0-100% [16], and 11% to 80% [27] have been reported by local and international studies. Amikacin with a resistance rate of 2.9% and meropenem with a resistance rate of 8.5% were the most active drugs against Gram- negative bacteria. Our result was in good agreement with the findings of earlier studies conducted in in Turkey [33] and India [26]. Amikacin and meropenem were the most active drugs against almost all Gram- negative bacteria.

Multi- drug -resistant profile of Gram- positive and Gram-negative bacteria are shown in table 4 and 5, respectively. The clinical isolates such as *P. aeruginosa*, Methicillin Resistant *S. aureus* (MRSA), *Enterococci* especially Vancomycin Resistant *Enterococci* (VRE), and members of Family Enterobacteriaceae have been recognized as the most common and serious multi-drug -resistant pathogens [20]. This was evident by the present study. Out of 29 isolate of Gram-positive bacteria, 16 (55.2%) were MDR, of which 11 (35.9.3%) were XDR and 2 (6.9%) were PDR. Among 15 isolates of *S. aureus* 5 (33.3%), 3 (20%), and 2 (13.3%) were MDR, XDR, and PDR, respectively. Six (75%) and 3 (37.5%) out of 8 isolates of coagulase negative staphylococci, were MDR and XDR respectively. Of 5 isolates *Enterococcus* sp. 5 (100%) and were MDR and 3 (60%) XDR. Similarly, of 35 isolates Gram-negative bacteria, 26(74.3%) were MDR and 18 (54.4%) were XDR. Furthermore out of 11 isolates of *K. pneumoniae* all (100%) isolates were MDR of which 9 (81.8%) were XDR.

Bacterial Isolate	Multi drug resistance %									
	R_0	R_1	R_2	R_3	R_4	R_5	R_6	n (%) MDR	n (%) XDR	n (%) PDR
S. aureus (n = 15)	1	6	3	0	1	2	2	5 (33.3%)	3 (20%)	2 (13.3%)
CONS (n = 8)	0	1	1	3	1	2	0	6 (75%)	3 (37.5%)	0
Enterococcus (n = 5)	0	0	0	2	3	0	0	5 (100)	3 (60%)	0
S. pneumoniae (n = 1)	0	1	0	0	0	0	0	0	0	0
Total (29)	1	8	4	5	5	4	2	16 (55.2%)	11 (37.9%)	2 (6.9%)

Table 4: *Multi drug resistance pattern of Gram -positive bacterial isolates from blood culture.*

R0: No antibiotic resistant; R1: Resistant to one antimicrobial category R2: Resistant to two antimicrobial categories; R3: Resistant to three antimicrobial categories; R4: Resistant to four antimicrobial categories; R5-resistant to five antimicrobial categories; R6: Resistant to six antimicrobial categories.

Bacterial Isolate	Multi drug resistance									
	R_0	R_1	R_2	R_3	R_4	R_5	R_6	n (%) MDR	n (%) XDR	n (%) PDR
K. pneumoniae (n = 11)	0	0	0	2	7	2	0	11 (100%)	9 (81.8%)	0
Enterobactercloacae (n = 5)	1	1	3	0	0	0	0	0	0	0
E. coli (n = 4)	1	0	0	2	0	1	0	3 (75%)	1 (25%)	0
K. oxytoca (n = 2)	0	0	0	0	1	1	0	2 (50%)	2 (50%)	0
Citrobacter (n = 1)	0	0	0	0	1	0	0	1 (100%)	1 (100%)	0
Serratia marcescens (n = 1)	0	0	0	1	0	0	0	1 (100%)	0	0
P. aeruginosa (n = 4)	0	0	1	2	1	0	0	3 (75%)	1 (25%)	0
Acinetobacter (n = 7)	1	0	1	1	1	1	2	5 (71.4%)	4 (57.1)	0
Total (35)	3	1	5	8	11	5	2	26 (74.3%)	18 (54.4%)	0

Table 5: *Multi-drug resistance pattern of Gram: negative bacterial isolates from blood culture.*

R0: No antibiotic resistant; R1: Resistant to one antimicrobial category R2: Resistant to two antimicrobial categories; R3: Resistant to three antimicrobial categories; R4: Resistant to four antimicrobial categories; R5-resistant to five antimicrobial categories; R6: Resistant to six antimicrobial categories.

Conclusion

The magnitude of blood stream bacterial infection and the prevalence rate of multi-drug resistant bacterial strains causing blood stream infections were high. These findings warranted the need for continuous investigations of bacteria implicated in causing blood stream infection and evaluation of their antibiotic susceptibility profile in health institution large scale.

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Conflict of Interest

The work does not have financial and/or non-financial competing interest. The author declares that there is no conflict of interest regarding the publication of this paper.

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