Original Article

J Nepal Health Res Counc 2024 Jul.-Sept.;22 (64): 574-581

Bloodstream Infections in a Nepalese Tertiary Hospital-Aetiology, Drug Resistance and Clinical Outcome

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ABSTRACT

Background: Bloodstream infections (BSIs) are a leading cause of sepsis-related morbidity and mortality globally. We present the pathogenic agents of bloodstream infections, their antimicrobial susceptibilities, and associated outcomes, with a focus on drug-resistant cases.

Methods: We included all adult patients admitted to B.P. Koirala Institute of Health Sciences with blood culture-positive sepsis from July 2019 to June 2020. Blood cultures and antimicrobial susceptibility tests followed standard methods. Demographic, clinical, and microbiological data, including clinical outcomes, were documented. Patients were categorized into non-multidrug resistant (non-MDR), multidrug resistant (MDR), and extensively drug resistant (XDR) groups for analysis of clinical outcomes.

Results: Of 5372 adult patients with suspected bloodstream infections, 475 (9%) had culture-positive infections with 536 organisms cultured. The median age of the patients was 42 (25-60) years, and 47% of the patients were women. There were 146 (31%) non-MDR, 220 (46%) MDR and 109 (23%) XDR cases. Common pathogens were *Staphylococcus aureus* (27%), *Acinetobacter spp* (20%), and *Klebsiella spp* (15%). The overall in-hospital mortality rate was 8% (38/475). Mortality was highest among XDR patients (53%), compared to MDR (29%) and non-MDR patients (18%) ($p < 0.001$). Patients in XDR group had longer hospital stays compared to MDR-BSI and non-MDR BSI patients ($p=<0.001$). After adjusting for risk factors, the odds ratio for in-hospital mortality in XDR patients was 2.52 (CI 1.11–5.72, $p = 0.02$).

Conclusions: Drug-resistant pathogens are prevalent in our setting, causing bloodstream infection. Extensively drug-resistant bacteria in the blood are independently and significantly linked to increased mortality.

Keywords: Bloodstream infections; clinical outcome; drug resistance.

INTRODUCTION

Bloodstream infections (BSIs) are a leading cause of sepsis-related morbidity and mortality globally.[1] While they are a major cause of mortality in Europe,[2] data on BSI in developing countries are limited. These data are crucial for guiding prompt and effective antimicrobial treatment to prevent the life-threatening consequences of septicemia. World Health Organization has identified antibiotic resistance among top ten global health threats.[3] Few studies on BSI from Nepal have reported the gram-negative bacteria predominance with notable resistance patterns.[4-6] Multidrug-resistant (MDR) organism infections pose a serious threat to patient outcomes.[7-10] It's unclear if resistance patterns directly lead to higher mortality rates, as some studies offers contradictory findings.[11-12] We present the pathogens causing BSIs, their susceptibility to antimicrobials, and associated outcomes, with a focus on drug-resistant cases, from a tertiary hospital. Our secondary objective was to identify risk factors associated with in-hospital mortality in patients with BSI.

METHODS

This is a prospective cohort study conducted at the BP Koirala Institute of Health Sciences hospital in Dharan,

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Nepal, from July 2019 to June 2020. The study aimed to investigate bacterial bloodstream infections in adult patients admitted to the hospital. Patients with positive blood cultures were included in the study, while duplicate blood samples from the same patient were excluded. A standard data collection form was used to collect basic demographic, clinical, and microbiological data, including sex, age, duration of hospitalization, comorbidity, presenting signs and symptoms, isolated organism, and their sensitivity pattern. We documented clinical outcomes, including improvement, in-hospital mortality, and length of hospital stay (LOS).

Approximately 5-10 ml of venous blood was aseptically collected from adult patients with signs of sepsis and inoculated into brain heart infusion (BHI) broth. The cultures were incubated aerobically at 35°C for 24 hours. After this, aliquots were subcultured onto sheep blood and MacConkey agar plates and monitored for up to 96 hours. Colonies were then identified using standard microbiological techniques, including colony morphology, gram staining, and various biochemical tests (catalase, coagulase, oxidase, sulfide indole motility, citrate, triple sugar iron, and urease tests).[13]

Antibiotic susceptibility testing of the isolates was performed using the modified Kirby-Bauer disk diffusion method, according to Clinical and Laboratory Standards Institute (CLSI) guidelines,[14] with quality control ensured by using Escherichia coli ATCC 25922 and Staphylococcus aureus ATCC 25923. A bloodstream infection (BSI) episode was defined as the isolation of the same organism from one or more positive blood bottles with no symptoms between isolations. Bacterial isolates were classified as multidrug-resistant (MDR) or extensively drug-resistant (XDR) based on criteria from the European Centre for Disease Prevention and Control and the Centers for Disease Control and Prevention.[15]

Multidrug resistance (MDR) was defined as non-susceptibility to ≥1 agent in ≥3 antimicrobial categories and extensively drug-resistant (XDR) as susceptibility limited to ≤ 2 categories.[15] Methicillin-resistant staphylococcus aureus (MRSA) defined as cefoxitin-resistant strains, and MRSA was considered MDR. We compared various clinical outcomes among three groups: non-MDR, MDR, and XDR. Ethical clearance was obtained from Institutional review board of BPKIHS Dharan.

Data were entered into MS Excel 2007 and analyzed using STATA version 14 (Stata Corporation, College Station, TX, USA). The distribution of data normality was evaluated with histograms, skewness-kurtosis, and the Shapiro-Wilk test. For comparing nonparametric data across three groups, the Kruskal-Wallis test was used. Categorical data were analyzed with the chi-square test or Fisher's exact test, as appropriate. Univariate and multivariate logistic regression analyses were performed to compare hospital mortality between groups. Results are reported as median (IQR), number (percentage), and odds ratio (95% confidence interval), with a p-value of <0.05 considered statistically significant.

RESULTS

Of the total of 5372 adult patients with suspected episodes of BSI admitted to the hospital, 475 (9%) had blood culture-positive BSI episodes with 536 organisms cultured (Figure 1). Forty-seven percent of the patients were women, with a median age of 42 years (25-60 y). Comorbidities were noted in 152 patients (34%). Among the 475 patients, there were 220 cases of MDR (46%) and 109 cases of XDR (23%) (Table 1).

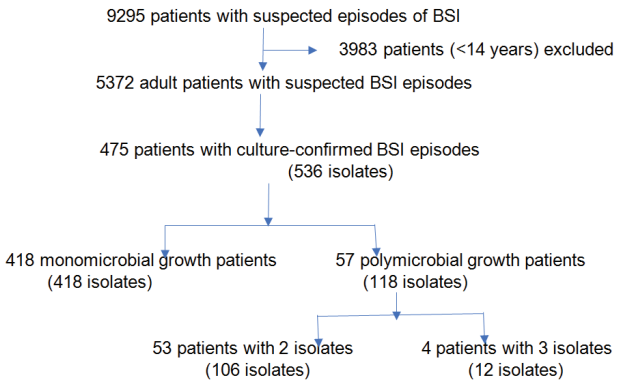

Figure 1. Flow chart of patients with bloodstream infection.

Table 1. Clinical characteristics and outcome of study population. (n = 475)

Variables	Culture confirmed BSI episodes	
	n	%
Female	224	47
Median age (range)	42(25-60)	
Co-morbidity		
Diabetes	57	12
Renal disease	43	9
Liver disease	39	8
Others	13	3
Non-MDR cases	146	31

Table 1. Clinical characteristics and outcome of study population. (n = 475)

Variables	Culture confirmed BSI episodes	
	n	%
MDR cases	220	46
XDR cases	109	23
ICU admission	84	18
Improved	437	92
In-hospital mortality	38	8
Hospital stays (days)	9(7-13)	-

As shown in Table 2, Gram-negative pathogens were the predominant cause of BSI, accounting for 346 out of 536 cases (65%). The most common pathogens overall included *Staphylococcus aureus* 147 (27%), *Acinetobacter spp* 107(20%), *Klebsiella spp* 81(15%), *Pseudomonas spp* 74(14%) and *Escherichia coli* 59(11%). Of 190 isolates of gram-positive bacteria, 92 (48%) and 22(12%) were MDR and XDR, respectively. Similarly, of 346 gram-negative bacteria isolates, 134 (39%) were MDR and 103 (30%) were XDR. Table 3 shows the results of the *in vitro* drug sensitivity testing among gram-positive pathogens. MRSA was present in 96(65%) *S. aureus*. Gram-negative pathogens were found to have varying degrees of antimicrobial resistance to commonly used antibiotics aminoglycosides, fluroquinolones, cotrimoxazole, and chloramphenicol ranging from 20-75% (Table 4).

Table 2. Bacterial isolates associated with bloodstream infections. (n-536)

Bacterial Isolates	Isolates n (%)	MDR strains n (%)	XDR strains n (%)
Gram Positive isolates	**190 (35%)**	**92(48%)**	**22(12%)**
Staphylococcus aureus	147 (27%)	88(60%)	13(7%)
Enterococcus faecalis *Enterococcus faecium*	22(4%) 20 (3.5) %	3(14%) 1(5%)	5(23%) 4(20%)
Streptococcus pyogenes	1 (0.2%)	-	-
Gram negative isolates	**346 (65%)**	**134 (39%)**	**103 (30%)**
Acinetobacter baumannii *Acinetobacter species*	54(10 %) 53(10 %)	29(54%) 8(15%)	18(41%) 13(25%)
Klebsiella pneumoniae *Klebsiella oxytoca*	73(14 %) 8 (1.5%)	35(48%) 1(13%)	25(40%) -
Pseudomonas aeruginosa *Pseudomonas spp*	54(10 %) 20(4 %)	23(43%) 3(15%)	18(41%) 5(25%)
Escherichia coli	59 (11%)	24(41%)	17(29%)
Citrobacter freundii	15(3 %)	6(40%)	5(33%)
Enterobacter aerogenes	10(2 %)	5(50%)	2(20%)
Total	536(100%)	226(42%)	125(23%)

MDR: Multidrug-resistant, XDR: Extensive drug-resistant

Table 3. Resistance percentage of Gram-positive isolates.

Antimicrobial agents	*S. aureus*	*E. faecalis*	*E. faecium*
	n=147, RI (%)	n=22, RI (%)	n=20, RI (%)
Ampicillin	-	8(36%)	11(55%)
Penicillin	179 (91%)	9(41%)	11(55%)
Amoxyclav	171 (87%)	-	-
Cephalexin	46%	-	-
Cefoxitin	65%	-	-
Cotrimoxazole	39%	-	-
Any fluroquinolones	23%	8(38%)	10(50%)

Table 3. Resistance percentage of Gram-positive isolates.

Antimicrobial agents	*S. aureus*	*E. faecalis*	*E. faecium*
Any macrolides	66%	15(68%)	16(80%)
Any aminoglycosides	66%	10(45%)	11(50%)
High-level gentamycin	-	7(32%)	9(45%)
Vancomycin	0%	0%	0%
RI=Resistant Isolates			

Table 4. Resistance percentage of common Gram-negative isolates.

Antimicrobial agents	*K. pneumoniae*	*E. coli*	*A. baumannii*	*P.aeruginosa*	*C. freundii*	*E. aerogenes*
	n=73, RI (%)	n=59, RI (%)	n=54, RI (%)	N=54, RI (%)	n=15, RI (%)	n=10, RI (%)
Penicillin	-	48 (81%)	-	51(95%)	12(80%)	7 (70%)
Amoxyclav	-	-	-	-	-	-
Ampisulbactam	-	-	22(41%)	-	-	-
PIT	63 (86%)	22 (37%)	18 (33%)	35(65%)	5(33%)	2 (13%)
3rd generation cephalosporin	58 (79%)	41(69%)	49 (91%)	48 (89%)	13 (87%)	8 (80%)
Aminoglycosides	55(75%)	0 (0%)	14 (26%)	11(20%)	3(20%)	5 (50%)
Fluroquinolones	52(71%)	37 (63%)	11 (20%)	26(48%)	3 (20%)	3 (30%)
Cotrimoxazole	55(75%)	19 (32%)	0 (0%)	-	10 (67%)	5 (50%)
Chloramphenicol	26 (35%)	14 (24%)	21 (39%)	-	8 (53%)	5(50%)
Carbapenam	45 (62%)	12(20%)	27 (50%)	32 (59%	5 (33%)	4 (40%)
Tigecycline	31(42%)	0 (0%)	8(15%)	-	3 (20%)	2 (20%)
Colistin	0 (0%)	-	0 (0%)	0 (0%)	0 (0%)	0 (0%)
RI=Resistant Isolates						

Regarding the clinical outcome among patients with BSI, the overall in-hospital mortality rate was 38/475 (8%). The mortality rate of XDR-BSI patients 20(53%) was significantly higher than that of MDR-BSI 11(29%) and non-MDR patients 7(18%) (p=<0.001). Similarly, hospital stay was significantly longer in patients with XDR-BSI [16 (11-19)] compared to patients with MDR-BSI [8.5(7-10)] and non-MDR BSI [8 (7-10)] (p=<0.001) patients. Table 5 presents the results of the univariate and multivariate logistic regression analyses for variables associated with in-hospital mortality. After adjusting for independent risk factors, the odds ratio (OR) for in-hospital mortality was 0.38 (95% CI: 0.14-1.03, p = 0.05) in the MDR-BSI group compared to cases without MDR-BSI, while in the XDR-BSI group, the OR was 2.52 (95% CI: 1.11-5.72, p = 0.02).

Table 5. Univariate and multivariate logistic regression for risk factors associated with in-hospital mortality.

Variables	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
Age	1.01 (0.99-1.03)	0.05	0.985 (0.96-1.008)	0.221
Sex				
Male	Reference			
Female	1.59(0.81-3.12)	0.17	1.789 (0.87-3.66)	0.221
Any Comorbidities				

Table 5. Univariate and multivariate logistic regression for risk factors associated with in-hospital mortality.

Variables	Univariate analysis		Multivariate analysis	
Present	Reference	<0.001		
Absent	1.25(2.35-11.72)		7.230 (2.60-20.05)	<0.001
Cases				
Non-MDR	Reference			
MDR	0.40 (0.15-1.06)	0.06	0.384 (0.142-1.035)	0.059
XDR	2.75 (1.26-6.03)	0.01	2.525 (1.112 -5.729)	0.027

Non-MDR=non-multi-drug resistant, MDR=multi-drug resistant, XDR- extensively drug resistant

DISCUSSION

The current study was conducted to examine the distribution of bacterial isolates causing BSIs in adult patients, their antibiotic resistance patterns, and the associated clinical outcomes. Our report underscores the prevalence of MDR and XDR bacteria that cause BSI in adult patients, highlighting their substantial influence on treatment outcomes.

Our study observed an incidence of 9% BSI among clinically suspected patients, which was comparable to other studies from Nepal reported by Parajuli et al. (7.4%),[4] Simkhada et al. 7.2%),[16] Khanal et al. (10.3%)[17] and Pandey et al. (12.6%).[18] But it was lower than the culture positivity rate documented from the neighboring countries India (22.3%),[19] and Pakistan (16%),[20]. This variation in culture positivity may be due to the difference in sampling volume of blood culture, culture system, and geographical location. We observe a shifting trend in the etiology of BSIs, where gram-negative bacteria are increasingly predominant, while gram-positive isolates, particularly *Staphylococcus aureus*, also play a substantial role. Our findings of gram-negative predominance concur with those reported in previous studies from Nepal by Parajuli et al. (65.8%),[4] Ranjit et al. (81.05%),[6] Simkhada et al. (78.6%)[16] and Khanal et al. (60%).[17] The most commonly isolated gram-negative bacteria included *Acinetobacter spp.*, *Klebsiella spp.*, *Pseudomonas spp.*, and *E. coli*. Studies from western Nepal[21] and central Nepal[4,6,17] corroborate our findings on the spectrum of organisms involved in these studies. However, they had a notable presence of *Salmonella enterica*, which was not isolated in our research. These findings suggest that the eastern region of Nepal does not have the burden of enteric fever compared to other regions within Nepal.

The irrational and increased use of broad-spectrum antibiotics resulting in a surge in MDR pathogens is an emerging problem.[22] Our study showed a high proportion of MDR (42%) and XDR (23%) isolates. A similar trend of MDR infections was previously reported in other studies in Nepal[4,23] and India.[24] Among *S. aureus*, 60% were MDR and 65% were MRSA, which was higher than previous published reports from Nepal.[4,25] Prior antibiotic use is the most common risk factor for colonization and MRSA infection. Among gram-negative isolates, the overall pattern of susceptibility to antibiotics suggests a remarkable proportion of XDR organisms in our hospital. The isolation of XDR strains in BSIs is a serious issue as therapeutic options become very limited.

The antibiotic susceptibility patterns among gram-negative isolates indicate a significant proportion of XDR organisms in our hospital. The presence of XDR strains in bloodstream infections is particularly concerning, as it drastically limits treatment options. When comparing the resistance profile between pathogens, the XDR rate was higher in *P. aeruginosa*, *A. anitratus* and *K. pneumoniae*. A study from Poland[26] reported that more than 75% of non-fermenters causing BSIs are XDR. Non-fermenters resistant to carbapenem and Enterobacterales featured prominently in this study and were consistently reported by other studies.[4,6,27] The rise in antibiotic resistance in Nepal is driven by several factors, including widespread use in communities, inappropriate antibiotic practices in healthcare settings, and misuse in agriculture.

A key finding of our study was that BSI caused by MDR bacteria did not have a significant effect on in-hospital mortality. A similar finding was also reported by Blot et al., where resistance did not correlate with increased mortality.[12] However, this observation contrasts with other studies[28-29] which have reported that MDR infections were associated with higher mortality rates. This difference in the study findings from ours could be due to undifferentiation between MDR and XDR bacteria in other studies. Notably, our study demonstrated that XDR infections were independently linked to higher hospital mortality. Our findings are in concordance with

a previous study from Italy which reported that mortality was associated with XDR infections, but not with MDR infections.[30] The limited antimicrobial options for the treatment of XDR cases may explain the reason for its significant association with mortality.

This study has some limitations. We did not differentiate BSI as acquired in the community or hospital. Due to resource constraints, MIC testing for colistin, as recommended by CLSI, could not be done. However, our report provides relevant data that may be used to guide empirical therapy in this hospital or serve as a baseline for future research. Finally, our study was carried out in a single center and we recommend future multicenter studies for a more comprehensive understanding of the prevalence and dynamics of drug-resistant BSI in our country.

CONCLUSIONS

Our study showed that the incidence of blood culture positive BSIs among clinically suspected adults was 9%. While gram-negative bacteria (65%) were the leading cause of BSI, *Staphylococcus aureus* were the most commonly identified bacteria (27%) followed by *Acinetobacter spp* (20%) and *Klebsiella spp* (15%).

Of total, there were 35% non-MDR, 46% MDR, and 23% XDR cases. The overall mortality rate in hospital was 8%. The mortality rate and the hospital stay of XDR-BSI patients was significantly higher than those of patients with MDR-BSI and patients without MDR. The presence of XDR bacteria in the blood was independently and significantly associated with in-hospital mortality.

CONFLICT OF INTEREST

There are no conflicts of interest.

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