

MICROBIOLOGICAL PROFILE AND ANTIBACTERIAL RESISTANCE PATTERN OF GRAM-NEGATIVE BLOOD ISOLATES IN A TERTIARY CARE CENTRE IN NORTHERN INDIA

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Abstract

Bloodstream infections (BSIs) are one of the most frequent infections and a potentially lethal condition with a case fatality rate of 20–50%. The present study was done to determine the prevalence and antimicrobial resistance pattern of gram-negative bacteria in blood stream infections (BSI) in a tertiary care center in Northern India.

Methods- This was an observational study of antibiotic susceptibility data of gram-negative bacilli causing blood stream infections. 1939 blood cultures were received in the Department of Microbiology over a period of 1 year. Automated blood culture method was used (BacT/Alert3D). Bacterial identification as well as antibiotic-sensitivity was done using Vitek-2 automated systems.

Results- Out of the 1939 blood cultures received in the microbiology lab, 283 (14.6%) showed positive culture growth, 1136 (58.6%) were sterile and 520 (26.8%) were found to be contaminated. 140 (49.5%) cultures were found positive for gram-negative rods (GNR), 90 (31.8%) for gram-positive cocci and 53 (18.7%) for yeast-like candida. Among GNR, *Klebsiella pneumoniae* was the most common (20.1%), followed by *Escherichia coli* (7.7%), *Actinobacter baumannii* (7.4%), *Salmonella* species (5.3%), *Enterobacter cloacae* complex (3.1%), and *Pseudomonas* species (3.1%). Most of the *Klebsiella* species were found to be multi-drug resistant

(MDR), with resistance rates observed against Ampicillin, Ceftriaxone, Cefepime, Piperacillin+Tazobactam, Meropenem, Ciprofloxacin, Amikacin & Cotrimaxazole as 57.8%, 57.8%, 42%, 50.8%, 54.3%, 52.6%, 47.3%, & 45.6% respectively. Similarly, resistance rates observed for *E. coli* against same antibiotics were 63.6%, 41%, 50%, 32%, 36%, 59%, 18%, & 50% respectively.

Conclusion- *Klebsiella pneumoniae* was found to be the leading cause of BSI among GNR in our set-up. Report of MDR organisms causing BSI is a cause for concern. Moreover, 26.8% of the samples were found to be contaminated, which is a high number, demonstrating the need for improved sampling and handling methods.

KEYWORDS: Blood stream infection (BSI), Gram-negative bacteria, GNR, *Klebsiella pneumoniae*, multi-drug resistant (MDR)

INTRODUCTION

Worldwide, infectious diseases continue to rank first in terms of death, morbidity, and disability and extended hospital stays. High infection rates pose a risk to the public's health. Gram-negative bacteria are more prevalent in bacteremia and are responsible for 45% of community-acquired infections and 25% of nosocomial infections (1). *Escherichia coli*, *Pseudomonas*, *Klebsiella*, *Serratia*, *Salmonella*, *Enterobacter*, and other common gram-negative bacteria are to blame for bacteremia (2). Whereas the three main gram-positive bacterial species that can enter the circulation after an infection are *Staphylococcus*, *Streptococcus*, and *Enterococcus* (3).

Bloodstream infections (BSIs), which are one of the most frequent infections, are a potentially lethal condition with a case fatality rate of 20–50% (4). BSI can be a self-limiting infection or it could be as fatal as sepsis. These are a major global contributor to sepsis-related morbidity and mortality (5). The majority of the antibiotics regularly used to prevent and cure bacterial infections are in danger of losing their effectiveness due to the evolving epidemiology and susceptibility patterns of microorganisms (6).

Multidrug-resistant (MDR) infections have become more prevalent over time in both community and hospital settings in India. Globally, antibiotic resistance is a serious issue. Bacteria that are resistant to antibiotics result in 23,000 deaths annually. While Europeans and Americans use 1st or 2nd generation antibiotics, the Indian subcontinent uses 3rd or 4th generation antibiotics (7).

India is a developing country and it is a hub for emerging infections and the problem of increasing resistance and its changing patterns is serious because it is one of the causes of failure of treatment. The present study was done to evaluate the microbiological profile and antimicrobial resistance pattern of pathogens isolated from the blood samples of the patients from a tertiary care center in North India.

METHODOLOGY

This was a retrospective cross-sectional study of antibiotic susceptibility data of gram-negative bacilli causing bloodstream infections. A total of 1939 blood cultures were received in the Department of Microbiology of Jawaharlal Nehru Medical College and Hospital, AMU over a period of 1 year. Blood samples were collected under strict aseptic precaution before starting antimicrobial therapy and immediately inoculated into BacT/Alert3D blood culture bottle. For up to 5 days, bottles were incubated in the BacT/Alert3D (bioMérieux) automated system. Positive samples identified by the machine were immediately inoculated into 5% sheep blood, MacConkey agar, and chocolate agar. Standard bacteriological techniques were used to identify bacterial pathogens, and were confirmed by VITEK-2 (bioMérieux) automated systems. Antibiotic-sensitivity was done using VITEK-2 automated system and results were interpreted as per CLSI 2022 guidelines (8). The definition of Multi-drug resistant (MDR) by CDC is an isolate that is resistant to at least one antibiotic in three or more drug classes (9). As a result, the need for non-susceptibility to at least three types of antibiotics were chosen as the definition of MDR.

RESULTS

A total of 1939 blood culture samples were received in the enteric lab over a period of 1 year. Out of which 283 (14.6%) showed positive culture growth, 1136 (58.6%) were sterile and 520 (26.8%) were found to be contaminated. Out of 283 positive cultures 140 (49.5%) were gram-negative rods (GNR), 90 (31.8%) showed growth for gram-positive cocci (GPC) and 53 (18.7%) yeast-like

candida respectively. Among GNR, *Klebsiella pneumoniae* was the most common (57, 20.1%), followed by *Escherichia coli* (22, 7.7%), *Acinetobacter baumannii* (21, 7.4%), *Salmonella* species (15, 5.3%), *Enterobacter cloacae* complex (9, 3.1%), *Pseudomonas* species (9, 3.1%), *Burkholderia cepacia* (4, 1.4%), *Citrobacter* (2, 0.7%) and *Morganella morgani* (1, 0.3%) (Figure1).

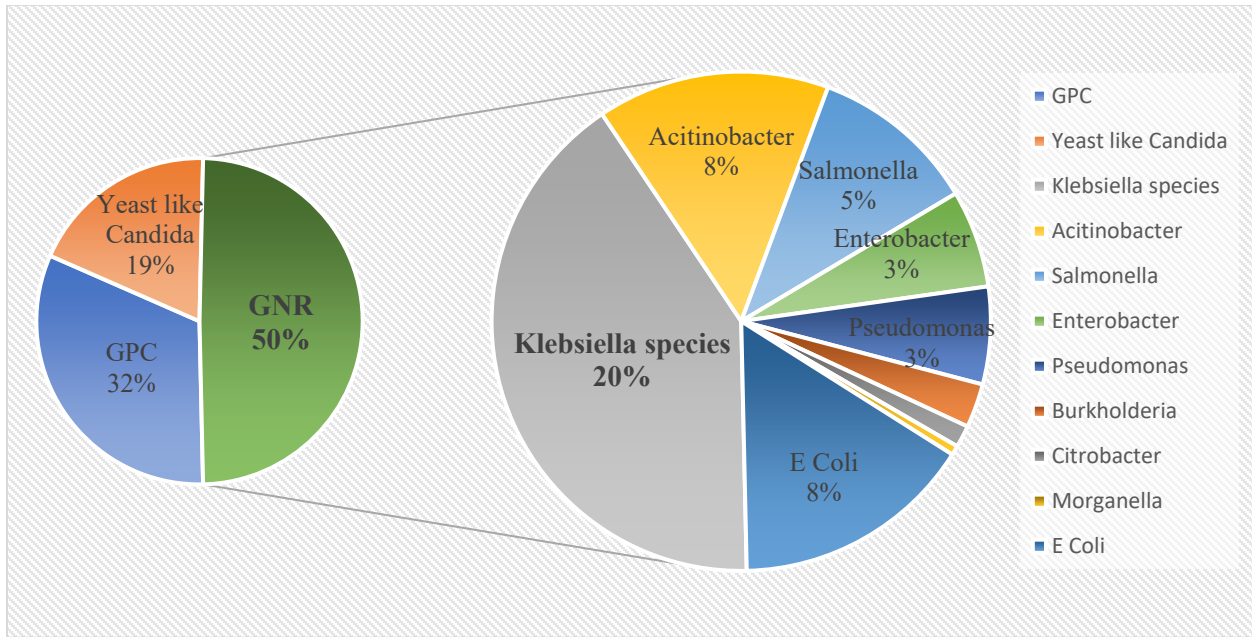


Figure 1 depicting the positive culture growths seen in blood cultures samples

Table1: Antibiotic Resistant rates of the isolated organisms

Resistant rates	Amc n (%)	Pit n (%)	Amp n (%)	Cfz n (%)	Ctr n (%)	Cfs n (%)	Cpm n (%)	Ipm n (%)	Mrp n (%)	Ak n (%)	Gen n (%)	Cip n (%)	Cot n (%)
Klebsiella species (n=57)	28 (49.1)	29 (50.8)	33 (57.8)	30 (52.6)	33 (57.8)	27 (47.3)	24 (42)	25 (43.8)	31 (54.3)	27 (47.3)	28 (49)	30 (52.6)	26 (45.6)
E. coli (n=22)	9 (41)	7 (32)	14 (63.6)	12 (54.5)	9 (41)	5 (22.7)	11 (50)	5 (22.7)	8 (36)	4 (18)	9 (41)	13 (59)	11 (50)
Acinetobacter baumannii (n=21)	1 (4.7)	11 (52.3)	0	10 (47.6)	11 (52.3)	9 (43)	11 (52.3)	10 (47.6)	12 (57)	-	10 (47.6)	10 (47.6)	10 (47.6)
Salmonella species (n=15)	1 (6.6)	1 (6.6)	2 (13.3)	1 (6.6)	3 (20)	1 (6.6)	1 (6.6)	0	3 (20)	6 (40)	7 (46.6)	6 (40)	1 (6.6)
Pseudomonas species (n=9)	-	1	-	-	1	1	2	0	2	3	3	0	0

Enterobacter cloacae (n=9)	5	3	0	4	3	3	4	3	3	3	3	4	3
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Table Abbreviations: Amc : Amoxicillin + clavulanic acid; Pit : Piperacillin + tazobactam; Amp : Ampicillin; Cfz : Cefoperazone; Ctr : Ceftriaxone; Cfs : Cefoperazone + Sulbactam; Cpm : Cefepime; Ipm : Imipenem; Mrp : Meropenem; Ak: Amikacin; Gen : Gentamicin; Cip : Ciprofloxacin; Cot : Co-trimaxazole

On antimicrobial susceptibility testing, most of the *Klebsiella* species were found to be multi-drug resistant (MDR), with resistance rates observed against Ampicillin, Ceftriaxone, Cefepime, Piperacillin+Tazobactum, Meropenem, Ciprofloxacin, Amikacin & Cotrimaxazole as 57.8%, 57.8%, 42%, 50.8%, 54.3%, 52.6%, 47.3%, & 45.6% respectively. Similarly, resistance rates observed for *E. coli* against same antibiotics were found to be 63.6%, 41%, 50%, 32%, 36%, 59%, 18%, & 50% respectively. (Table)

Collectively *Enterobacterales* were the dominant group of GNR isolated from blood samples, most of which were found to be MDR. Maximum resistance was seen with ciprofloxacin 51.4%. Among beta-lactams, maximum resistance was seen with Ampicillin 47.5%, followed by Ceftriaxone 46.6% and Cefpodoxime 45.6%. 40% of them were found to be ESBL producers. Carbapenems were found to be resistant in 32% (Imipenem) and 43.6% (Meropenem) of isolates. Among Aminoglycosides, Amikacin was found to be resistant in 39% and Gentamicin in 45.6%. Fortunately, none of the isolate was found to be resistant with Colistin. (Figure2)

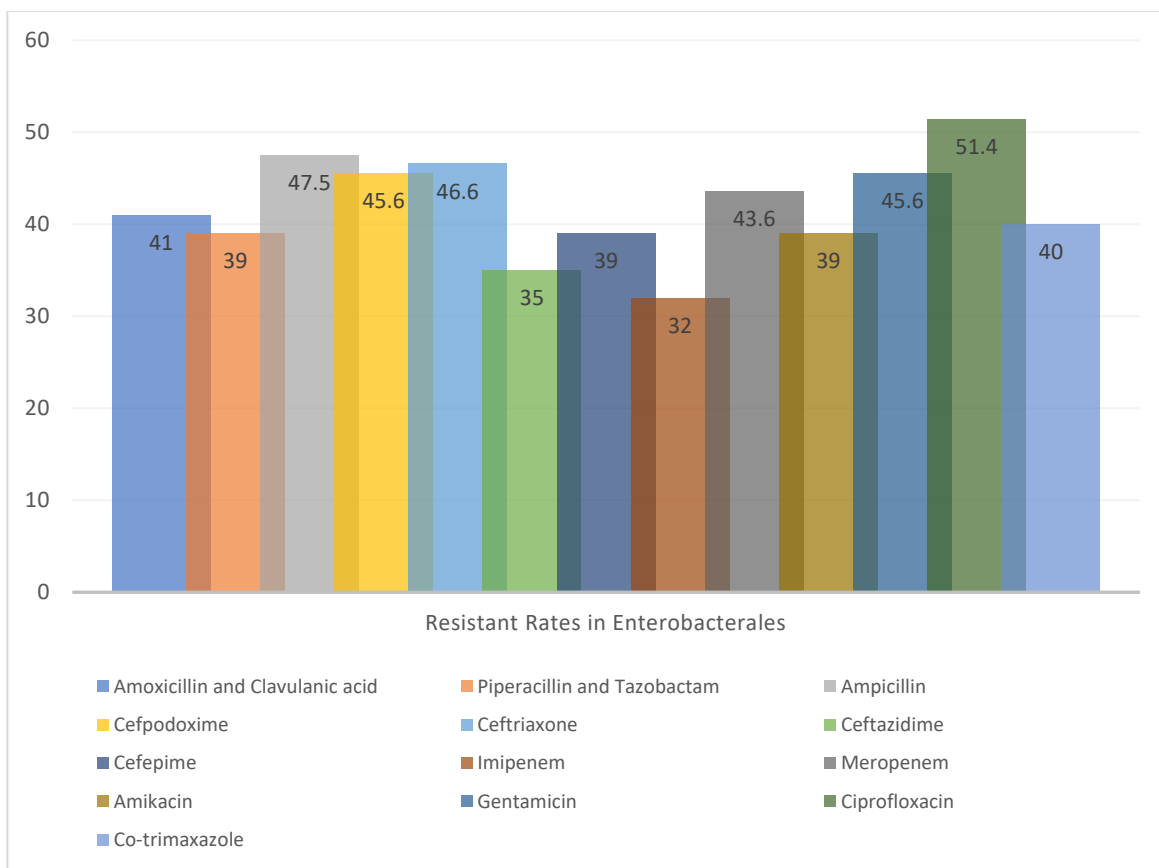


Figure2: Resistance rates in *Enterobacteriales*

Generally, the highest resistance to antimicrobials for gram-negative pathogens were seen towards: ampicillin, ceftriaxone, meropenem, cefuroxime axetil, cefotaxime and ciprofloxacin by *Klebsiella* species with 57.8%, 57.8%, 54.3%, 52.6%, 52.6% and 52.6%, respectively; ampicillin, ciprofloxacin, cefuroxime axetil and cefotaxime by *Escherichia coli*, 63.6%, 59.0%, 54.5% and 54.5%, respectively; meropenem, ceftriaxone, cefepime, Piperacillin+Tazobactum by *Acinetobacter* species, 57.0%, 52.3%, 52.3% and 52.3% respectively; gentamicin, amikacin, ciprofloxacin and cefuroxime axetil by *Salmonella* species, 46.6%, 40.0%, 40.0% and 26.6% respectively; gentamicin and amikacin by *Pseudomonas* species, 33.33% and 33.33%, respectively; and amoxicillin/ clavulanic acid and cefuroxime axetil by *Enterobacter* species, 55.5% and 55.5%, respectively.

Moreover, *Klebsiella* species was found to be highly resistant to Piperacillin + Tazobactum (50.8%), gentamicin (49%), amikacin and cefoperazone (47.3% each); *E. coli* demonstrated 50.0% resistance against cefepime and trimethoprim each; 47.6% *Acinetobacter* species were resistant to cefotaxime, gentamicin, ciprofloxacin and trimethoprim each; *Salmonella* species to ceftriaxone

and meropenem (20.0% each); and *Enterobacter* species to cefotaxime, cefipime and ciprofloxacin (44.4% each).

Fortunately, none of the GNR isolated was found to be resistant with Colistin, except *Burkholderia cepacia*, where it is intrinsically resistant.

DISCUSSION

The culture positivity rate for the present study was 283 (12.5%) which was higher as compared to the previous studies done in India by Rani N et al 8.3% & Gohel K et al 9.9% (10,11). Although it is quite similar to the positivity rates in Nigeria 13.1% (12), and also quite similar to our previous report of 13.6% positivity rate from the same institute in the year 2015 (13). This rate was higher as compared to other studies conducted in countries like Jimma & Cambodia 8.8% (14), and Tanzania 5.6% (15). It was lower than those reported in Lebanon 18.6% (16), Turkey 21.3% (17), India 22.3% (18), Ethiopia 18.2% (19) and 28% (20), Zambia 24% (21), Dhaka 14.38% (22), Zanzibar 14% (23) and Pakistan 16% (24). These differences in result could probably be due to variation in sample size, study design, location of study, epidemiological factors, causative agents, number and methods used for blood culture, volume of blood drawn and lack of clinical indication of BSI.

Total 140/283 (49.5%) cultures were found positive for gram-negative rods (GNR), 90/283 (31.8%) for gram-positive cocci (GPC) and 53/283 (18.7%) for yeast-like candida. Similar trend of GNR predominance is depicted by studies from Cambodia, Cote d' Ivoire, Ethiopia and Afghanistan (14,25–27). In contrast, GPC predominance was observed in various studies from Ethiopia, Zambia and USA (19–21,28). The fluctuation in results can be attributed to diversity of causative agents and epidemiological factors.

The predominant bacterial isolate among GNR was found to be *Klebsiella pneumoniae* 57 (20.1%). This finding was in agreement with numerous studies previously done in other countries(12,15,23,27,29). Similarly in the previous study from our institute *Klebsiella pneumoniae* was the most common isolate (13). This was followed by *Escherichia coli* 22 (7.7%) and *Acinetobacter baumannii* 21 (7.4%). A similar trend of prevalence was observed in Ethiopia and USA (26,28). In contrast to this study, a larger proportion of *Pseudomonas* species were

isolated among other gram negative bacteria in various studies from India and Ethiopia (11,18,19). Furthermore, different studies from numerous countries had reported *Salmonella* species among the top 3 most isolated gram-negative bacteria in blood isolates (10,14,17,20,21,23). *Acinetobacter* was the most common pathogen isolated causing BSI in a study by Khurana S et al., in India (30) and *E. coli* was found to be the most prevalent organism in a study done by Oyekale et al., in a tertiary hospital in Nigeria (31), whereas in our scenario *E.coli* is the second most prevalent organism isolated but *Klebsiella* species was isolated as second most common in the study by Khurana S et al. (30). These variations can be attributed to differences in geographic location and infection control policies practiced in various countries.

In our study *Klebsiella* species showed the highest resistance towards ampicillin and ceftriaxone (57.8% each), whereas *E. coli* demonstrated it towards ampicillin (63.6%) and ceftriaxone (41%). Study done in India by Rani V et al. demonstrated maximum resistance to cefotaxime by *Klebsiella* species and ampicillin by *E. coli* which is comparable to our study (10). *Klebsiella* species showed least resistance to ticarcillin and ceftriaxone-sulbactam and *E. coli* to ticarcillin, ceftazidime and levofloxacin. A study conducted by Gohel K. et al. highlighted that carbapenems were the most effective agent against *Klebsiella*, while carbapenems and aminoglycosides were most effective agents against *E. coli* (11). A study done in Ethiopia reported that the majority of *Klebsiella* species were resistant to ampicillin, ceftriaxone and amoxicillin- clavulanate which is quite close to results of our study (32). The highest resistance shown towards *E. coli* by the study done in Ethiopia and Nepal (32,33) is identical to our study.

Likewise to our study, others also found that most of the GNR causing BSI were multi-drug resistant (MDR) (4,20), with as high as 74.3% of GNR reported as MDR by Eshetu et al in 2018 (26). Such increasing trend in MDR bacteria causing BSI is a cause of concern as they are associated with poor outcomes, high cost and prolonged hospital stay if not properly and timely treated.

Some of the limitations of this study include short duration, uni-centric, small sample size and its study design. Poor sample collection technique and non-adherence of hospital staff to infection control practices while handling patient's samples is proven by a lot of contaminated samples and commensals detected, therefore hindering the accuracy of the results. Regional surveillance and

studies, such as ours, should be done from time to time in order to address the looming problem of changing epidemiology of BSI and changing trends in antibiotic resistance patterns. These regional trends and resistance pattern from such localized studies may be extrapolated to study the general population of India. Further multi-centric studies for longer duration are needed to study microbiological profile and drug resistance pattern of all blood isolates. This will help in implementing infection prevention and control strategies targeted to reduce blood stream infections.

Conclusion

Klebsiella pneumoniae was found to be the leading cause of BSI among GNR in our set-up. Report of MDR organisms causing BSI is a cause for concern. The knowledge of microbial profile is crucial for management of bloodstream infections. The antibiotic resistance pattern changes from hospital to hospital in the same country and continuously changes over time therefore antimicrobial resistance patterns will help us better in choosing appropriate drugs for treatment. Moreover, 23.0% of the samples were found to be contaminated, which is a high number, demonstrating the need for improved sampling and handling methods.

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