Section: Microbiology

Original Research Article

PREVALENCE, ANTIMICROBIAL SUSCEPTIBILITY, AND GENOTYPIC CHARACTERIZATION OF GRAM-NEGATIVE BACTERIA CAUSING BLOODSTREAM INFECTIONS IN PEDIATRIC AND NEONATAL ICUS AT A TERTIARY CARE HOSPITAL IN EASTERN INDIA

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Abstract

Background: Bloodstream infections (BSIs) are a critical cause of morbidity and mortality in healthcare-associated infections globally. In pediatric and neonatal intensive care units (ICUs), BSIs lead to extended hospital stays, increased healthcare costs, and significant mortality, particularly due to multidrug-resistant (MDR) organisms. This study aims to identify Gram-negative bacteria causing BSIs and determine their antimicrobial susceptibility patterns using automated culture systems. **Materials and Methods:** A prospective study was conducted from November 2023 to July 2024 in the Department of Microbiology at S.C.B. Medical College, Cuttack, involving 558 pediatric patients, including neonates, suspected of having BSIs. Blood samples were collected aseptically and processed using the BacT/ALERT 3D system. Positive cultures were further analyzed for microbial identification and antimicrobial susceptibility, with MDR strains tested for Extended Spectrum Beta-Lactamase (ESBL) production using phenotypic and genotypic methods. **Result:** Out of 558 suspected cases, 192 (34.4%) were culture positive, with Gram-negative bacteria isolated in 97 (50.5%) cases. Among these, 75 (77.3%) were MDR. The predominant MDR isolates were Acinetobacter baumannii (32%) and Klebsiella pneumoniae (22.6%). High resistance was noted to Piperacillin/Tazobactam (96%) and cefepime (90%). Phenotypic ESBL detection identified 36% of isolates, while genotypic methods confirmed 100% ESBL production. TEM gene predominance was observed in 100% of ESBL producers. Carbapenemase production was identified genotypically in 38.6% of isolates, with the NDM-1 gene present in 29 isolates. **Conclusion:** The study highlights the significant presence of MDR Gram-negative bacteria in pediatric BSIs and underscores the necessity for early diagnosis and appropriate antimicrobial therapy. Continuous surveillance of antimicrobial resistance patterns is crucial to guide effective treatment strategies and limit the spread of resistant strains.

INTRODUCTION

Bloodstream infection (BSI) is a significant cause of morbidity and mortality in healthcare-associated infections worldwide, with the etiology, antimicrobial susceptibilities, and outcomes varying by region. BSIs are life-threatening infections in hospitals, leading to prolonged hospital stays, high healthcare costs, and significant mortality, with approximately 200,000 cases annually and a mortality rate ranging from 20-50% worldwide.[1,2]

In the United States, BSIs are the 10th leading cause of death, with an incidence ranging from 76 to 100 cases per 100,000 people.[3,4] They are the most frequent nosocomial infections (28%) in ICUs of pediatric patients. Risk factors for BSIs in children include central venous catheters, parenteral nutrition, gastrointestinal pathology, especially short gut syndrome, and the use of broad-spectrum antibiotics.[5,6] In neonates, BSIs are less well characterized but are linked to the increased survival of extremely premature infants, dependence on catheters, parenteral nutrition, and antibiotic therapy. Neonatal BSIs vary from 4 to 24% of all bloodstream infections.[5-7]

BSIs denote the presence of viable organisms in the blood, with or without clinical symptoms. In contrast, systemic inflammatory response syndrome (SIRS) is defined by specific clinical criteria, and its combination with the presence of organisms is termed sepsis. Severe sepsis involves organ dysfunction, while septic shock is severe sepsis with hypotension unresponsive to fluid resuscitation. Sepsis significantly contributes to death in ICUs of neonates and pediatric patients.[8,9] The incidence of severe sepsis is influenced by age, sex, and race, being higher in infants, males, and blacks.[10] Risk factors include immunodeficiency, cancers, and the use of immunosuppressants, with severe sepsis resulting from both community-acquired and healthcare-associated infections. Multidrug-resistant microorganisms, surgical procedures, and invasive techniques are also risk factors.[10,11]

A wide range of organisms, predominantly Gram-negative bacteria, causes BSIs. Common pathogens include Escherichia coli, Pseudomonas aeruginosa, Klebsiella spp., Haemophilus influenzae, and various streptococci and staphylococci species.[12,13] Early diagnosis and treatment are crucial to reduce BSI-related morbidity and mortality. Automated culture systems like the BacT/Alert 3D/60 provide rapid and accurate detection of microorganisms, improving patient management through early confirmation and appropriate antimicrobial therapy.[14]

Despite advances in diagnostic microbiology, automated blood culture techniques are recommended for diagnosing bacteremia in tertiary care settings to reduce result generation time, improve patient outcomes, and cut costs associated with prolonged hospital stays. However, the high infrastructure costs are a drawback for many developing countries.[15]

Increasing antimicrobial resistance is a global concern, driven by acquired and innate resistance mechanisms. Resistance genes are often transferred horizontally via plasmids or bacterial genomes, necessitating constant antimicrobial sensitivity surveillance to inform empirical therapies and prescribing practices.[16]

This prospective study, carried out in the Department of Microbiology at S.C.B. Medical College, Cuttack, aims to isolate and identify Gram-negative bacteria causing bloodstream infections in pediatric and neonatal ICUs and to determine the antimicrobial susceptibility patterns of the isolated organisms using automated culture systems.

MATERIALS AND METHODS

This prospective study was conducted in the Department of Microbiology in S.C.B. Medical College and Hospital, Cuttack, Odisha. The study was carried out from November 2023 to July 2024. The study group comprised 558 pediatric patients, including neonates, who were clinically suspected of having bloodstream infections.

Inclusion Criteria

All clinically suspected cases of bloodstream infection admitted to the pediatric and neonatal intensive care units of the tertiary care hospital were included.

Exclusion Criteria

Samples from patients who had received antibiotics within 7 days prior to clinical presentation were excluded.

After selecting the cases, detailed clinical histories were obtained. Clinical parameters such as age, sex, and clinical presentation were recorded.

Sample Collection: Two sets of blood specimens were collected aseptically from 558 clinically suspected bloodstream infection patients. In each set, 2-4 ml of blood was collected into BacT/ALERT PF Plus culture bottles from two different body sites (right and left cubital fossa) with an interval of 15-30 minutes. Blood samples in BacT/ALERT culture bottles were loaded into the automated BacT/ALERT 3D system (bioMerieux, USA) and incubated at 37°C for up to 5 days. Positive culture bottles were sub-cultured on blood agar and MacConkey agar and incubated at 37°C for 24-48 hours.

Results were categorized as sensitive (S), intermediate (I), or resistant (R). Minimum inhibitory concentration (MIC) was detected using the micro broth dilution method, and resistant patterns were analyzed using the Advanced Expert Study (AES) system. DNA quality and quantity were measured using a UV-VIS Spectrophotometer, with a good quality DNA ratio between 1.8 and 2.0.

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RESULTS

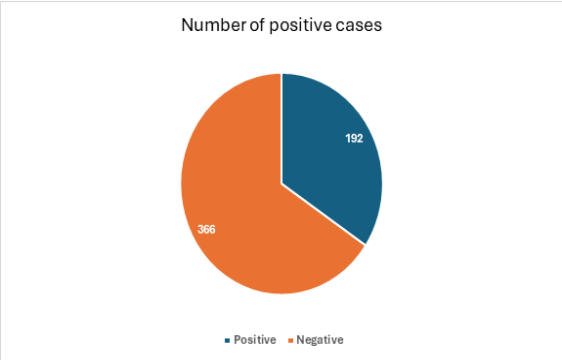

Figure 1: Culture positive cases among clinically suspected cases of sepsis

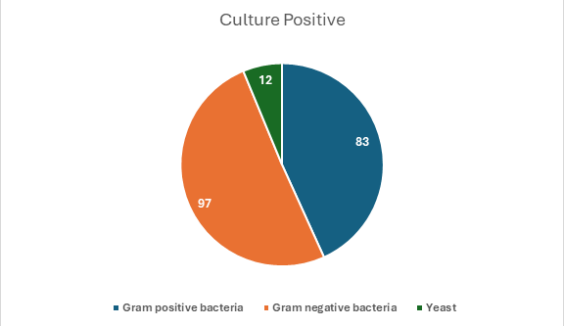

Figure 2: Distribution of microorganism among culture positive cases

Out of 558 clinically suspected sepsis cases, 192 (34.4%) were culture positive, while 366 (65.6%) were culture negative [Figure 1].

Among the 192 culture positive cases, Gram negative bacteria were the most common, accounting for 97 (50.5%) cases. Gram positive bacteria were isolated in 83 (43.3%) cases, and yeast was identified in 12 (6.2%) cases [Table 2].

Of the 97 Gram negative isolates, 75 (77.3%) were multi-drug resistant (MDR), while 22 (22.7%) were non-MDR. Among the MDR Gram negative isolates, Acinetobacter baumannii was the most prevalent, with 24 (32%) cases, followed by Klebsiella pneumoniae with 17 (22.6%) cases. Other notable isolates included Burkholderia cepacia complex (12 cases, 16%) and Escherichia coli (6 cases, 8%). Several other species were also identified, each constituting a smaller proportion of the isolates [Table 3].

The resistance patterns among MDR Gram negative isolates varied by organism. Acinetobacter baumannii showed high resistance to Piperacillin/Tazobactam and Cefuroxime, both at 100%, and 95.8% resistance to Ceftriaxone.

Klebsiella pneumoniae exhibited 100% resistance to Ampicillin and 94.1% resistance to Cefoperazone /Sulbactam [Table 4 and 5].

A total of 75 isolates were tested for Extended Spectrum Beta-Lactamase (ESBL) production by both phenotypic and genotypic methods. The phenotypic method detected 27 (36%) ESBL producers, whereas the genotypic method (detecting the TEM gene) identified all 75 (100%) isolates as ESBL producers. Notably, 100% of Acinetobacter baumannii, Klebsiella pneumoniae, Burkholderia cepacia complex, Escherichia coli, and several other species were confirmed as ESBL producers by the genotypic method [Table 6].

Among the gram negative isolates, Acinetobacter baumannii found highly resistant to Piperacillin/ Tazobactam (100%) & Cefuroxime(100%) followed by Ceftriaxone(95.8%), Similarly Klebsiella pneumoniae were highly resistant to ampicillin(100%), followed by Cefoperazone/ Sulbactam (94.1%). 27 (36%) isolates were detected as ESBL producer by phenotypic methods (Combined double disc test) but 75(100%) isolates were detected as ESBL producer by genotypic methods.

Table 1: Culture Positive Cases among Clinically Suspected Cases of Sepsis (n =558)

No. of cases	Number(%)
Positive	192(34.4%)
Negative	366(65.6%)
Total	558(100%)

Out of 558 clinically suspected sepsis cases, 192(34.4%) were culture positive.

Table 2: Distribution of Microorganism Among Culture Positive Cases (n=192).

Microrganism isolated	Number (%)
Gram positive bacteria	83(43.3%)
Gram negative bacteria	97(50.5%)
Yeast	12(6.2%)
Total	192(100%)

In blood culture out of 192 culture positive cases, Gram negative bacteria were 97(50.5%), followed by Gram positive bacteria 83(43.3%) & Yeast 12(6.2%).

Table 3: Distribution of Gram negative MDR isolates (n=75).

SL No	Organism	Number (%)
1	Acinetobacter baumannii	24(32%)
2	Klebsiella pneumoniae	17(22.6%)
3	Burkholderia cepacia complex (BCC)	12(16%)

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4	Escherichia coli	6(8%)
5	Enterobacter aerogenes	2(2.6%)
6	Enterobacter cloacae	2(2.6%)
7	Pantoea agglomerans	2(2.6%)
8	Acinetobacter lwoffii	2(2.6%)
9	Citrobacter freundii	2(2.6%)
10	Salmonella typhi	2(2.6%)
11	Acinetobacter junii	1(1.3%)
12	Klebsiella oxytoca	1(1.3%)
13	Citrobacter koseri	1(1.3%)
14	Pseudomonas aeruginosa	1(1.3%)

Table 4: Pattern of antimicrobial resistance among MDR gram negative isolates

Antibiotics	**Organism**						
	Acinetobacter baumannii (n =24)	**Klebsiella pneumonia (n =17)**	**Burkholderia cepacia complex (n=12)**	**Escherichia coli (n=6)**	**Enterobacter aerogenes (n=2)**	**Enterobacter cloacae (n=2)**	**Pantoea agglomerans (n=2)**
Ampicillin	NA	17(100%)	NA	6(100%)	NA	NA	NA
Amoxycillin/ Clavulanic acid	NA	15(88.2%)	NA	6(100%)	2(100%)	2(100%)	2(100%)
Piperacillin/ Tazobactam	24(100%)	15(88.2%)	12(100%)	6(100%)	2(100%)	2(100%)	2(100%)
Cefuroxime	24(100%)	14(82.3%)	NA	6(100%)	2(100%)	2(100%)	2(100%)
Cefuroxime Axetil	24(100%)	14(82.3%)	NA	6(100%)	2(100%)	2(100%)	2(100%)
Ceftriaxone	23(95.8%)	16(94.1%)	12(100%)	5(83.3%)	1(50%)	2(100%)	2(100%)
Cefoperazone/ Sulbactam	19(79.1%)	16(94.1%)	12(100%)	5(83.3%)	1(50%)	1(50%)	1(50%)
Cefepime	21(87.5%)	14(82.3%)	12(100%)	5(83.3%)	2(100%)	2(100%)	2(100%)
Ertapenem	22(91.6%)	5(29.4%)	NA	5(83.3%)	2(100%)	2(100%)	2(100%)
Imipenem	21(87.5%)	13(76.4%)	12(100%)	3(50%)	2(100%)	2(100%)	2(100%)
Meropenem	22(91.6%)	14(82.3%)	1(8.3%)	6(100%)	2(100%)	2(100%)	2(100%)
Amikacin	9(37.5%)	7(41.1%)	12(100%)	5(83.3%)	2(100%)	2(100%)	2(100%)
Gentamicin	18(75%)	10(58.8%)	12(100%)	5(83.3%)	1(50%)	2(100%)	2(100%)
Nalidixic acid	NA	6(35.2%)	NA	6(100%)	NA	NA	2(100%)
Ciprofloxacin	21(87.5%)	3(17.6%)	12(100%)	6(100%)	2(100%)	2(100%)	2(100%)
Tigecycline	2(8.3%)	0(0%)	1(8.3%)	0(0%)	0(0%)	0(0%)	0(0%)
Colistin	0(0%)	0(0%)	12(100%)	0(0%)	0(0%)	0(0%)	0(0%)
Trimethoprim-Sulfamethoxazole	19(79.1%)	6(35.2%)	1(8.3%)	3(50%)	0(0%)	1(50%)	2(100%)

Table 5: Pattern of Antimicrobial resistance among MDR gram negative isolates

Antibiotics	**Organism**						
	Acinetobacter lwoffii (n=2)	**Citrobacter freundii (n=2)**	**Salmonella typhi (n=2)**	**Acinetobacter junii (n=1)**	**Klebsiella oxytoca (n=1)**	**Citrobacter koseri (n=1)**	**Pseudomonas aeruginosa (n=1)**
Ampicillin	NA	NA	2(100%)	NA	1(100%)	NA	NA
Amoxycillin/ Clavulanic acid	NA	NA	2(100%)	NA	1(100%)	NA	NA
Piperacillin/ Tazobactam	2(100%)	2(100%)	2(100%)	1(100%)	1(100%)	1(100%)	0(0%)
Cefuroxime	2(100%)	NA	2(100%)	NA	1(100%)	NA	NA
Cefuroxime Axetil	2(100%)	NA	2(100%)	NA	1(100%)	NA	NA
Ceftriaxone	2(100%)	NA	2(100%)	1(100%)	1(100%)	NA	NA
Cefoperazone/ Sulbactam	2(100%)	2(100%)	1(50%)	1(100%)	1(100%)	1(100%)	1(100%)
Cefepime	2(100%)	2(100%)	2(100%)	1(100%)	1(100%)	1(100%)	1(100%)
Ertapenem	NA	2(100%)	2(100%)	NA	1(100%)	1(100%)	NA
Imipenem	2(100%)	2(100%)	2(100%)	1(100%)	1(100%)	1(100%)	1(100%)
Meropenem	2(100%)	2(100%)	2(100%)	1(100%)	1(100%)	1(100%)	1(100%)
Amikacin	2(100%)	2(100%)	2(100%)	1(100%)	1(100%)	1(100%)	1(100%)
Gentamicin	1(50%)	NA	2(100%)	1(100%)	1(100%)	NA	1(100%)
Nalidixic acid	NA	NA	0(0%)	NA	1(100%)	NA	NA
Ciprofloxacin	2(100%)	NA	0(0%)	1(100%)	1(100%)	NA	1(100%)
Tigecycline	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	1(100%)
Colistin	1(50%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	1(100%)
Trimethoprim-Sulfamethoxazole	2(100%)	0(0%)	0(0%)	1(100%)	1(100%)	0(0%)	NA

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Table 6: Comparison of ESBL by Phenotypic and Genotypic method

SL No	Organism	Number	Phenotypic method	Genotypic Method (TEM Gene)
1	Acinetobacter baumannii	24	8(33.3%)	24(100%)
2	Klebsiella pneumoniae	17	12(70.5%)	17(100%)
3	Burkholderia cepacia complex	12	0(0%)	12(100%)
4	Escherichia coli	6	5(83.3%)	6(100%)
5	Enterobacter aerogenes	2	0(0%)	2(100%)
6	Enterobacter cloacae	2	2(100%)	2(100%)
7	Pantoea agglomerans	2	0(0%)	2(100%)
8	Acinetobacter lwoffii	2	0(0%)	2(100%)
9	Citrobacter freundii	2	0(0%)	2(100%)
10	Salmonella typhi	2	0(0%)	2(100%)
11	Acinetobacter junii	1	0(0%)	1(100%)
12	Klebsiella oxytoca	1	0(0%)	1(100%)
13	Citrobacter koseri	1	0(0%)	1(100%)
14	Pseudomonas aeruginosa	1	0(0%)	1(100%)
	Total	75	27(36%)	75(100%)

DISCUSSION

Bloodstream infections (BSI) remain a significant cause of morbidity and mortality among pediatric patients. Prompt clinical suspicion, early diagnostic measures, timely initiation of rational antimicrobial therapy, and comprehensive supportive measures are crucial for the successful management of BSI.[17] Blood cultures play a pivotal role in diagnosing and managing BSI.

In the present study, blood culture was positive in 192 (34.4%) of cases, which aligns with findings by Surase et al. (32%) and Parihar et al. (28.9%) [204, 205]. Various studies from different parts of India and around the world have shown varying blood culture positivity rates, such as Goel et al. (9.2%), Nasa et al. (10.6%), Mathur et al. (10.6%), Lunagaria et al. (16.9%), Arora et al. (20.02%), Sharma et al. (33.9%), and Remirez Barba et al. (39%).[18]

In our study, Gram-negative bacteria, Gram-positive bacteria, and yeasts were isolated in 50.5%, 43.3%, and 6.2% of cases, respectively, in automated blood culture systems. These findings are similar to those of Lunagaria et al., who isolated Gram-negative bacteria, Gram-positive bacteria, and yeasts in 55.3%, 40%, and 4.7% of cases, respectively.[19] Most studies have reported a higher prevalence of Gram-negative bacteria compared to Gram-positive bacteria.[20]

Our study observed that 75 (77.3%) of the Gram-negative bacteria isolated were multidrug-resistant (MDR), whereas the study by Gupta et al. reported a 72.1% MDR rate among Gram-negative bacteria isolates.[21] Acinetobacter baumannii (32%) was the predominant isolate, followed by Klebsiella pneumoniae (22.6%) in clinically suspected bloodstream infections. In contrast, Livadiotti et al. found Klebsiella pneumoniae (27%) as the most common isolate,[22] indicating possible geographical variation in the spectrum of microorganisms.

The antibiotic resistance pattern among Gram-negative isolates in this study showed that most isolates were resistant to Piperacillin/Tazobactam (96%) and cefepime (90%), similar to findings by Vanitha et al.[23] Among the Gram-negative isolates, Acinetobacter baumannii was highly resistant to Piperacillin/Tazobactam (100%) and Cefuroxime (100%), followed by ceftriaxone (95.8%). Similarly, Klebsiella pneumoniae showed high resistance to ampicillin (100%), followed by Cefoperazone/ Sulbactam (94.1%). Colistin (97.3%) and tigecycline (97.3%) were the most effective antibiotics for all Gram-negative bacterial isolates, including non-fermenters, aligning with Lunagaria et al., who found colistin (80.9%) and tigecycline (66%) as the most sensitive antibiotics.[24]

In this study, 36% of isolates were detected as Extended Spectrum β-Lactamase (ESBL) producers by phenotypic methods (Combined double disc test), while 100% of isolates were detected as ESBL producers by genotypic methods (targeting the TEM gene). Bajpai et al. reported 51.2% as ESBL producers by phenotypic methods and 48.7% by genotypic methods.[25] In our hospital settings, the TEM gene (100%) predominated over SHV (24%) and CTX (24%) genes responsible for ESBL production. This result aligns with Yazdi et al. (87.1% TEM, 70.6% SHV, 30.8% CTX) but differs from studies by Eftekhar et al., where SHV (43.1%) exceeded TEM (35.2%); Shahid et al., where CTX (28.8%) exceeded SHV (13.7%); and Ahmed et al., where CTX (71.4%) exceeded TEM (55.1%).[26] Several other studies worldwide have shown variable results.[27,28]

The higher incidence of ESBL production could be due to the injudicious use of antibiotics in hospitalized patients and geographic variation. Carbapenems are known as the last resort for treating infectious diseases, playing a key role in managing severe hospital-acquired infections. The recent emergence of carbapenemase-producing Gram-negative isolates mediating carbapenem resistance is a worrying trend.[29]

By phenotypic methods, we detected 27 (36%) isolates as ESBL producers, 4 (5.3%) as AmpC producers, and none as carbapenemase producers. However, genotypic methods detected 75 (100%) isolates as ESBL producers, 9 (12%) as AmpC producers, and 29 (38.6%) as carbapenemase producers. The higher incidence of MDR isolates

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with resistant genes may be due to the injudicious use of antibiotics and geographical variation.

CONCLUSION

In this study, we investigated the genotypic and phenotypic drug resistance patterns of Gram-negative bacteria isolated from bloodstream infections among pediatric patients in a tertiary care hospital in Odisha. The findings highlight a significant prevalence of multidrug-resistant (MDR) organisms, underscoring the critical need for continuous monitoring and stringent antibiotic stewardship. A substantial proportion of Gram-negative isolates exhibited resistance to multiple commonly used antibiotics, including third-generation cephalosporins and carbapenems. Klebsiella pneumoniae and Escherichia coli were the most frequently isolated organisms, with a high incidence of extended-spectrum beta-lactamase (ESBL) production. The presence of such resistant pathogens poses a serious challenge to the effective management of bloodstream infections in pediatric patients. Therefore, it is imperative to implement robust infection control measures, optimize antibiotic use, and promote ongoing surveillance to combat the rising threat of antimicrobial resistance in this vulnerable population.

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