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MICROBIAL PROFILE AND ANTIMICROBIAL SUSCEPTIBILITY PATTERN OF BLOOD ISOLATES OF CLINICALLY SUSPECTED CASES OF SEPTICAEMIA IN ICU

Medical Microbiology

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ABSTRACT

Context: Blood stream infections (BSI) is one of the most common cause of morbidity and mortality in critically ill patients admitted in intensive care unit (ICU). Infection with resistant microorganism are associated with high morbidity and mortality. Monitoring of the spectrum of pathogenic microorganism and their susceptibility pattern is important to helps in appropriate empirical treatment. **Objective:** The present study was undertaken to know the microbiological profile and antimicrobial susceptibility pattern of the isolated microorganism from blood of ICU patients to formulate effective empirical treatment. **Methodology:** A total of 140 blood cultures isolates were studied from various ICUs. The isolates were identified by standard microbiological procedures, and antibiogram was determined as per Clinical and Laboratory Standards Institute (CLSI) guidelines. **Results:** Of total 140 bacterial isolates, Gram-Negative Bacilli, Gram-Positive Cocci and Candida spp. contributed to (57.14%), (38.57%), and (4.28%) respectively. The predominant microorganisms were Klebsiella pneumoniae followed by Acinetobacter spp. and Staphylococcus aureus. Maximum number isolates were obtained from Adult ICU (57.14%) followed by NICU and PICU (21.42%) each. All GNB isolated were susceptible to Colistin (100%), tigecycline, minocycline. GPC isolated were completely susceptible to Vancomycin, Teicoplanin and Linezolid and 73.2% were MRSA. 73.75% GNB were MDR and 32% were ESBL producer. **Conclusion:** The knowledge of microbial profile and antibiogram of blood culture isolates is important to help the clinician to choose appropriate antimicrobials for early management of patients.

KEYWORDS

Bloodstream infection, MDR, ESBL

INTRODUCTION

Blood stream infections (BSI) is one of the most common cause of morbidity and mortality all around the world, especially in critically ill patients admitted in intensive care unit (ICU).[1-4] It is defined by isolation of live microorganisms in the bloodstream. The presence of viable bacteria in blood is termed as bacteraemia and the presence of multiplying bacteria in blood that may produce toxin is termed as septicaemia. BSI can be classified clinically into two stages on the basis of severity and the extent of organ failure into sepsis and septic shock.[5] Sepsis is a life-threatening organ dysfunction caused by dysregulated host response to infection and is characterised by systemic inflammatory response syndrome (SIRS).

SIRS criteria include -fever >38ºC OR <36ºC, tachypnoea >20 breaths/min, tachycardia with heart rate >90 beats/min, leukocytosis with WBC count >12000/µL or leukopenia <4000/ µL or >10% immature neutrophils.[6]

BSI can either be primary where the origin of infection is unclear or it can be secondary where transferring of pathogens from a local site of infection to another body site into the bloodstream can occur.[7] Enfeebled condition of the patient due to underlying diseases, invasive diagnostic and therapeutic procedures, contaminated life support devices, increased contact with healthcare personnel and length of stay in the ICU put these patients at high risk of infection to fatal BSI.[8]

Both Gram Positive and Gram-Negative bacteria have been implicated as the most common cause of septicaemia. The pattern of pathogens causing BSI has been changing over the years, with increasing numbers of Gram-negative microorganism and fungal infections.[9] There is an alarming increase in micro-organisms that are resistant to multiple antimicrobial agents at an alarming rate in the ICU setting resulting in high morbidity, mortality, and treatment costs.[10-11]

The current study was conducted to analyse the prevalent microorganisms causing blood stream infection (BSI) and their antimicrobial susceptibility pattern among ICU patients in a Tertiary care hospital, Jaipur.

MATERIALAND METHODS

This study was a laboratory based descriptive type of observational study and was carried out in the Department of Microbiology, Sawai Man Singh Medical (SMS) College, Jaipur (Rajasthan) from July 2021 to August 2022.

Blood culture bottles (for Paediatric patients BACT/ALERT PF PLUS and for adult patients BACT/ALERT FA PLUS) inoculated with blood samples from clinically suspected septicaemia cases from various ICUs of the hospital including Neonatal ICU, Paediatric ICU, Medical ICU, Surgical ICU and Trauma ICU were received in Microbiology Department.

Blood culture bottles received were loaded in Automated Blood culture system. (BACT/ALERT -An automated colorimetric microbial detection system) as per manufacturer's instructions.

A total of 140 positive flagged blood culture bottles were included in this study, after excluding bottle showing contaminants (Micrococci, Gram Positive Bacilli, diphtheroid and other contaminants).

These blood culture bottles were sub-cultured on MacConkey (MC) and Blood agar (BA) and other relevant media if required. Growth was identified on the basis of colony characteristics, Gram staining and biochemical reactions as per standard microbiological techniques.[12]

The antimicrobial susceptibility testing of isolates was performed by Kirby Bauer's disc diffusion method on Muller Hinton agar and was interpreted as per CLSI guidelines 2021.[13]

Multidrug resistant (MDR) was defined as acquired nonsusceptibility to at least one agent in three or more antimicrobial categories.[14]

Detection of Methicillin resistant Staphylococcus aureus (MRSA) was done using Cefoxitin (30 µg) disc. Extended spectrum β-lactamase (ESBL) production was detected with Ceftazidime (30 µg) and Ceftazidime + Clavulanic acid (30/10 µg) and were analysed as per CLSI guidelines.

Sample size was calculated at 95% confidence level, assuming alpha error of 0.05%. With 8% absolute allowable error the required sample size was calculated 140 culture positive isolates using the statistical formula for estimating proportions.

Relevant data from patients were collected and recorded on structured proforma.

The qualitative and quantitative data were analysed using appropriate statistical tests. P value <0.05 was taken as significant.

The study was conducted after getting approval from the institutional research review board and the ethical committee.

RESULTS

A total of 140 microorganism were isolated from blood culture bottles of 140 clinically suspected cases.

Maximum isolates were obtained from Medical ICU 45 (32.14%) followed by Trauma ICU 31 (22.14%), Neonatal ICU and Paediatric ICU 30(21.42% each) and Surgical ICU 4 (2.85%) as shown in Figure No 1.

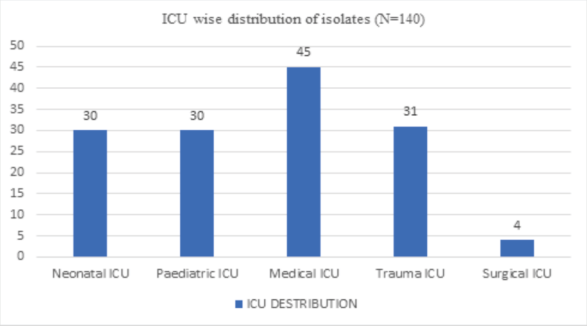

Figure No 1: ICU wise distribution of isolates.

Out of 140 microorganisms 93 (66.42%) were isolated from males and 47 (33.58%) from female. Male: female ratio was approximately 1.9:1. Maximum cases belong to the age group 19 - 40 years 38 (27.14%) followed by age group 0 - 28 days and >28 days -18 years (21.42 each). Among isolates from all ICUs, maximum isolates were Gram Negative Bacilli 80 (57.14%) followed by Gram Positive Cocci 54 (38.57%) and Candida spp. 6 (4.28%).

Of all 140 isolates, *Klebsiella pneumoniae* (24.28%) was the most frequently isolated microorganism followed by *Acinetobacter spp.* (20%), *Staphylococcus aureus.* (16.42%), Coagulase Negative Staphylococci (12.85%), *Enterococcus spp. & Escherichia. coli* (9.28% each) and *Pseudomonas aeruginosa* (3.5%). Candida spp. accounted for 6 (4.28%) as shown in Figure No 2.

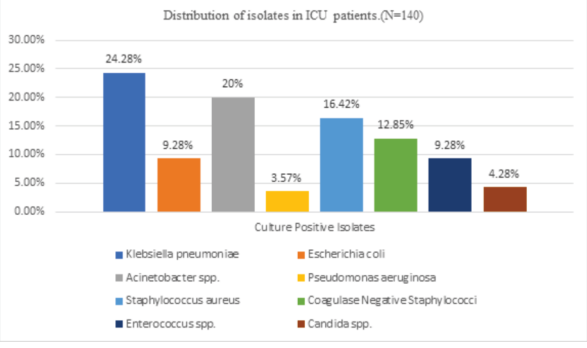

Figure No 2: Distribution of isolates in ICU patients.

Among the 80 Gram-Negative Bacilli, *Klebsiella pneumoniae* (42.5%) was the most frequent isolate followed by *Acinetobacter spp.* (35%), *Escherichia. coli* (16.25%), and *Pseudomonas aeruginosa* (6.25%).

Of 60 Gram Positive Cocci *Staphylococcus aureus* 23 (42.59%) was the most commonly isolated organism followed by Coagulase Negative Staphylococci (33.33%) and *Enterococcus spp.* 13 (24.07%). Further we observed that the distribution of pathogens in Paediatric ICUs differed from that in the adult ICU. Isolation of Gram-Positive Cocci was comparatively higher in paediatric ICU patients than adult ICU while Gram-Negative Bacilli were more common in adult ICU.

The ICU wise distribution revealed that the most predominant bacteria isolated from NICU and PICU was *Staphylococcus aureus* (9/30, 30.0%) and (7/30, 23.3%), followed by *Klebsiella pneumoniae* (6/30, 20%) in NICU and Coagulase Negative Staphylococci (7/30, 23.3%) in PICU. In adult ICU *Acinetobacter spp.* (24/80, 30%) was the most frequent organism isolated followed by *Klebsiella pneumoniae* (22/80, 27.5%). The various isolates obtained compared among neonates, paediatric and adult patients is depicted in Figure No 3.

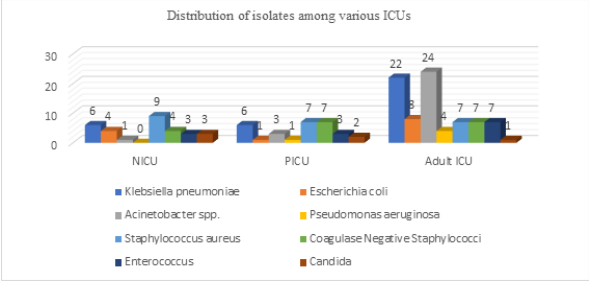

Figure No 3: Distribution of isolates among various ICUs

Pattern of antimicrobial susceptibility of Gram Negative and Gram-Positive organisms isolated in our study is shown in Tables 1 and 2. All Gram-Negative isolates were completely susceptible to Polymyxins 80 (100%), followed by Tigecycline and Minocycline 58 (77.33%) each. susceptibility to Imipenem was 28.75%. Third generation Cephalosporins showed lowest susceptibility ranging from (5.3% - 11.25%).

Table No 1: Antimicrobial susceptibility pattern of Gram-Negative bloodstream isolates. (in percentage)

Organisms / Antibiotics	Klebsiella pneumoniae (N=34)	E. coli (N=13)	Acinetobacter spp. (N=28)	Pseudomonas aeruginosa (N=5)	Total (N=80)
Ampicillin	0	1 (7.69%)	0	-	1/75 (1.33%)
Piperacillin + Tazobactam	5 (14.7%)	3 (23.07%)	2 (7.14%)	5 (100%)	15 (18.75%)
Cefotaxime	3(8.8%)	1 (7.69%)	0	-	4 (5.33%)
Ceftazidime	3 (8.8%)	1 (7.69%)	0	3 (60%)	7 (8.75%)
Cefoperazone + sulbactam	5(14.7%)	4 (30.76%)	6 (21.4%)	4 (80%)	19 (23.75%)
Cefepime	4 (11.76%)	2 (15.38%)	0	3 (60%)	9 (11.25%)
Imipenem	10 (29.41%)	8 (61.53%)	2 (7.14%)	3 (60%)	23 (28.75%)
Aztreonam	-	-	-	2 (40%)	2 (40%)
Polymyxin-B/ Colistin	34 (100%)	13 (100%)	28 (100%)	5 (100%)	80 (100%)
Amikacin	6 (17.6%)	3 (23.07%)	1 (3.57%)	3 (60%)	13 (16.25%)
Gentamicin	7 (20.58%)	3 (23.07%)	3 (10.7%)	3 (60%)	16 (20%)
Tobramycin	-	-	-	3 (60%)	3 (60%)
Tigecycline	22 (64.70%)	12 (92.23%)	24 (85.71%)	-	58 (77.33%)
Minocycline	24 (70.58%)	11 (84.46%)	23 (82.14%)	-	58 (77.33%)
Ciprofloxacin	8 (23.52%)	3 (23.07%)	3 (10.7%)	3 (60%)	17 (21.25%)
Cotrimoxazole	8 (23.52%)	2 (15.38%)	5 (17.85%)	-	15 (20%)

Gram-Positive Cocci were completely susceptible to Linezolid, Vancomycin and Teicoplanin (100% each) followed by Gentamicin 26 (63.41%) and Doxycycline 34 (62.96%). Least susceptibility was seen to Erythromycin 7(12.96%). A total of 2 (15.38%) of *Enterococci* were susceptible to Hight level Gentamicin. Methicillin resistance was observed in 73.2% isolates of *Staphylococcus aureus* (MRSA) and

55.56% in Coagulase negative Staphylococci (MRCoNS).

Table No 2: Antimicrobial Susceptibility Pattern Of Gram-positive Bloodstream Isolates. (in Percentage)

Organisms / Antimicrobial Agents	Staphylococcus aureus (N=23)	CoNS (N=18)	Enterococcus spp. (N=13)	Total (N=54)
Ampicillin	6 (26.08%)	7 (38.8%)	1 (7.69%)	14 (25.92%)
Cefoxitin	6 (26.08%)	8 (44.44%)	-	14 (34.14%)
Vancomycin	23 (100%)	18 (100%)	13 (100%)	54 (100%)
Teicoplanin	23 (100%)	18 (100%)	13 (100%)	54 (100%)
Gentamicin	15 (65.21%)	11 (61.1%)	-	26 (63.41%)
High-level Gentamicin	-	-	2 (15.38%)	-
Doxycycline	17 (73.91%)	15 (83.3%)	2 (15.38%)	34 (62.96%)
Erythromycin	1 (4.34%)	6 (33.3%)	0	7 (12.96%)
Linezolid	23 (100%)	18 (100%)	13 (100%)	54 (100%)
Ciprofloxacin	11 (47.82%)	9 (50%)	4 (30.76%)	24 (44.44%)
Cotrimoxazole	10 (43.47%)	11 (61.1%)	-	21 (51.21%)
Clindamycin	2 (8.6%)	12 (66.6%)	-	14 (34.14%)

Out of 80 Gram Negative Bacilli, 59 (73.75%) were Multi drug resistant (MDR) with maximum of *Acinetobacter spp.* (42.37%) followed by *Klebsiella pneumoniae* (37.28%), *Escherichia coli* (18.64%) and *Pseudomonas aeruginosa* (1.69%).

Out of 75 GNB (excluding *Pseudomonas spp*.) 24 (32%) were ESBL producers with maximum of *Acinetobacter spp.* (50%) followed by *Klebsiella pneuomoniae* (33.3%) and *Escherichia. coli* (16.6%).

Gram-Negative Bacilli and Gram-Positive Cocci isolated from cases of Paediatric and Neonatal ICU were more susceptible to antimicrobial agent tested than cases from Adult ICU, however this difference was not found to be statistically significant ($p > 0.05$) except for Gentamicin tested for Staphylococci where difference was significant ($p < 0.05$).

Table No 3: Antimicrobial Susceptibility Pattern Of Gram-negative Bloodstream Isolates Among Paediatric And Adult Age Group.

Distribution of isolates / Antimicrobial	Isolates from Children (N=22)	Isolates from Adults age group (N=58)
Ampicillin	1 (4.54%)	0
Piperacillin + Tazobactam	5 (22.72%)	10 (17.24%)
Cefotaxime	2/21 (9.52%)	2/54 (3.70%)
Ceftazidime	3 (13.63%)	4 (6.89%)
Cefoperazone + sulbactam	6 (27.27%)	13 (22.41%)
Cefepime	4 (18.18%)	5 (8.62%)
Imipenem	8 (36.36%)	15 (25.86%)
Aztreonam	0%	2/4 (50%)
Polymyxin-B	22 (100%)	54 (100%)
Amikacin	6 (27.27%)	7 (12.06%)
Gentamicin	7(31.81%)	9(15.51%)
Tobramycin	1(100%)	2/4(50%)
Tigecycline	18/21(85.71%)	40/54(74.04%)
Minocycline	18/21(85.71%)	40/54(72.22%)
Ciprofloxacin	8/22(36.3%)	9/58(15.51%)
Cotrimoxazole	4/21(19.04%)	11/54(20.37%)

A total of 6(4.28%) Candida spp. were isolated. Candida glabrata 4 (66.66%) was the most predominant Candida spp. isolated followed by Candida albicans and Candida krusei 1(16.6% each), Candida isolates were more among Paediatric age 5(83.3%) group than in adult group 1(16.6%).

Table No 4: Antimicrobial Susceptibility Pattern Of Gram-positive Bloodstream Isolates Among Paediatric And Adult Age Group.

Distribution of isolates / Antimicrobial	Isolates from Children (N=33)	Isolates from Adult age Group (N=21)
Ampicillin	12(36.36%)	2/21(9.52%)
Cefoxitin	12/27(44.44%)	2/14(14.2%)
Vancomycin	33(100%)	21(100%)
Teicoplanin	33(100%)	21(100%)
Gentamicin	15/27(55.5%)	11/14(78.5%)
High level Gentamicin	2/6(33%)	0/7(0%)
Doxycycline	23/33(69.6%)	11/21(52.3%)
Erythromycin	6/33(18.1%)	1/21 (4.7%)
Linezolid	33(100%)	21(100%)
Ciprofloxacin	19/33(57.5%)	5/21 (23.8%)
Cotrimoxazole	15/27(55.55%)	6/14(42.85%)
Clindamycin	13/27(48.14%)	1/14(7.14%)

DISCUSSION

The present study provides information regarding distribution of organisms isolated along with the antimicrobial susceptibility of microorganism isolated from septicemic patients admitted in ICUs, which plays a critical role in effective management of ICU patients. A wide range of microorganisms are responsible for BSIs. The prevalence, epidemiology and microbiological profile of BSIs differs from one country to another, institutions and also among ICUs within hospitals.

The present study included a total of 140 blood culture isolates from 140 clinically suspected patients of septicaemia admitted in various ICUs.

Gender based analysis revealed male preponderance with male: female ratio being 1.9:1 (male 66.42%, female 33.57%). The difference between gender and BSI was found to be statistically significant (P value<0.05). Male preponderance has also been reported in various other studies done by Nasa P et al[18], Savage R D et al[24] and Lachhab Z et al[30]

Majority of isolates were reported among age group 19 - 40 years (38, 27.14%) followed by paediatric age group [neonates and children >28 days (30, 21.42%)].

Out of 140, Gram Negative Bacilli (80/140, 57.14%) were found to be the predominant cause of bloodstream infection while Gram positive cocci accounted for 60 (42.86%). Various other studies from India and different parts of the world including Tabah A et al[21], Wattal C et al[22], Lone S M. et al[25], Ahsan A A et al[27], Lachhab Z et al[30], Gebre-egziabher T. S. et al[32] and Palewar M. et al[34] have also reported the higher rate of GNB over Gram-Positive Cocci. On the contrary Ahmed H S et al[15], Erdem I et al[16], Orsini J et al[20] and Savage D R et al[24] reported Gram-Positive isolates to be more frequent than GNB.

Among Gram-Negative Bacilli, *Klebsiella pneumoniae* 34 (24.28%) and *Acinetobacter* spp. 28 (20.0%) were the frequent isolates causing BSIs. These findings are in accordance with the finding of Wattal C. et al[22] and Sonawane P J et al[33]. Other GNB isolated were *Escherichia coli* 13(9.28%) and *Pseudomonas spp.* 5 (3.57%), which has also been reported by various authors in varying frequencies ranging from 2.3%-26.5% (Wattal C et al.[22], Gill K M et al[23], Katyal A et al[29], Palewar M et al[34].

Among Gram Positive Cocci, *Staphylococcus aureus 23 (*42.59%) was frequently isolated pathogen. Predominance of *Staphylococcus aureus* as a bloodstream pathogen has been documented by various other studies conducted by Lone S M. et al[25], Sangwan J et al.[26], and Palewar M. et al[34].

Coagulase Negative Staphylococci (CoNS) isolated in 12.85% of cases in our study which coincides well with various other studies (Savage D R et al[24], Lone S M. et al[25], Palewar M. et al[34]). A Higher rate Coagulase-negative Staphylococci have been reported by Wattal C et al[22], Katyal A et al[31]

Role of CoNS as BSI pathogen is controversial, CoNS isolates are often skin colonizers and appear in blood culture as common contaminants at the time of sample collection. However clinical relevance of a single blood culture positive for CoNS is difficult to assess, mainly because of the lack of a diagnostic reference standard for BSI. Clinical correlation of the blood culture isolate and determination of time to positivity of CoNS isolates can help to differentiate between potential contaminants and true pathogens L. Elzi et al[17] documented the Clinical significance of single blood culture positive for CoNS based on systemic inflammatory response (SIRS) criteria and presence of central venous catheter. in absence of central venous catheter SIRS criteria ≥3 SIRS criteria or SIRS criteria ≥2 with central venous catheter is considered probable true BSI with CoNS.[6].

Enterococci was isolated in 9.28% of cases in our study which is in accordance to study done by Tabah A et al[21], Moolchandani K et al.[29], Palewar M. et al[34]. Higher rate of isolation was reported by Orsini J et al[20] and Savage D R et al[26].

Microbial profile of septicaemia cases varies from ICU to ICU of same institute. On analysis of distribution of Gram-Negative Bacilli from various ICU, it was noted that GNB were more frequently isolated from Adult ICU (27%) as compared to paediatric ICU with *Acinetobacter spp.* and *Klebsiella pneumoniae* being predominant. While Gram-Positive Cocci (*Staphylococcus aureus* and Coagulase Negative Staphylococci) were predominantly isolated from blood culture from paediatric ICU.

Study documents the extent of antibiotic resistance among the frequently isolated organism. It is evident from Table No. 1 that Colistin, Tigecycline were the most effective antibiotic against GNB in our study.

Gram-Negative isolates showed a high susceptibility to Polymyxins (100%) which coincides with the susceptibility reported by Lone S M. et al[24].

In our study low susceptibility to Carbapenem (Imipenem) was observed (28.75%). Susceptibility rate of Carbapenems (Imipenem) have been decreasing over the years as observed from previous year studies which reported higher susceptibility rate than to our study ranging from 49% to 90%. (Ahmed H S et al[15], Erdem I et al.[16], Lone S M. et al[25])

Aminoglycosides tested showed susceptibility ranging from 16-20%. Higher susceptibility to Aminoglycosides than our study have been reported in previous study done by Erdem I et al.[16], Lone S M. et al[25], Palewar M et al.[34]

Third and Fourth generation Cephalosporins showed low susceptibility rate ranging from 8.75%-11.75%. which is comparable with the study by Palewar M et al[34] who reported it to be 23%.

Gram-Positive isolates showed highest susceptibility to Vancomycin, Teicoplanin and Linezolid which is comparable to other Indian studies done by Sweta O S. et al[20] and Savage D R et al[24]. However, Vancomycin and Teicoplanin resistance in enterococci have been documented by Palewar M. et al[34]. susceptibility rate to Aminoglycoside was documented to be 63.41% in the present study. Higher susceptibility (80%) have been reported by Palewar M. et al[34] Other group of antimicrobial agents including erythromycin and doxycycline clindamycin, showed susceptibility ranging from 12.96%-62.96% which is comparable with the study by Sangwan J et al[26].

Methicillin resistance was observed in 73.2% isolates of *Staphylococcus aureus* (MRSA) which is comparable with findings of Palewar M. et al[34] (70%). A Relatively low percentage of Methicillin resistance have been reported by Sangwan J et al[26] (58.4%) and Katyal A et al[31] (31.64%). Methicillin resistance among CoNS (MRCoNS) was observed to be 55.56%which is comparable with an Indian study done by Katyal A et al[31] (51.25%).

MDR organisms are becoming more common making choice of empirical antimicrobial therapy challenging. Our study documents a high proportions of the Gram-Negative isolates to be multidrug resistant (73.75%). Among Enterobacteriaceae, 37.28% of *Klebsiella pneumoniae* and 18.64% of the *Escherichia coli* and among non-fermenters 42.37% *Acinetobacter spp.* and 1.69% *Pseudomonas aeruginosa* were multidrug resistant (MDR).

Further it was observed that 24 isolates (32%) of Gram-Negative Bacilli were Extended spectrum β- lactamase (ESBL) producer which coincides with the findings of Orsini J et al[22]. However, a higher rate of ESBL producing organisms have been reported in other studies ranging 42.5 – 90.6% from India and worldwide (Nasa P et al.[18], Sweta O S et al.[28], Lachhab Z et al.[30], Gebre-egziabher T. S. et al[32] and Palewar M. et al[34])

The antibiotic susceptibility pattern of isolates also varies according to the patient age. In this study, isolates from paediatric patients were more susceptible to antimicrobial agent tested than the isolates from adult patients which is comparable with the study done by Ariffin N et al[19].

Variation in susceptibility pattern seen, may be due to type of ICU, empirical treatment and selection pressure of high end antimicrobial used in various ICU.

CONCLUSION

The present study highlights the high rate of isolation of MDR organisms from blood of septicaemia patients in various ICUs. Resistant strains are not only the major obstacle to the treatment but once established, infections are likely to lead to further transmission. Coordinated infection control intervention and antimicrobial stewardship policies are warranted in order to slow the emergence of resistance.

Ethics Statement

Informed consent and Institutional ethical clearance (Ethical clearance no 1190/MC/EC/2021 dated 03/12/2021) was obtained.

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