Original Research Article

Spectrum of Gram Negative organisms in an Adult ICU of a Tertiary Care hospital

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Abstract

Background: Infections play vital role in determining the outcome as well as cost and duration of the hospital stay for patients admitted in Intensive Care Unit (ICU) setup. One of the major problems Worldwide is the rise in Antibiotic-Resistant Strains of bacteria, mainly in hospitals. Infections frequently encountered with drug resistant organisms include those with Methicillin Resistance Staphylococcus aureus (MRSA), Extended-Spectrum β-Lactamase (ESBL), and Metallo β-Lactamase (MBL) producing organisms.Extended-spectrum β-lactamase (ESBL) producing strains of Enterobacteriaceae have emerged as a challenge in hospitalized patients as well as in the community. **Objectives:** 1. To isolate and identify bacterial pathogens in Adult Intensive Care Unit (ICU). 2. To study antimicrobial susceptibility patterns of gram negative organisms isolated from samples in Adult ICU. 3. To detect presence of Extended Spectrum β Lactamases in all Enterobacteriaceae isolates. **Material and methods:** Depending on sites of infections various samples were collected and processed for bacterial identification and antibiotic susceptibility as per the standard guidelines. **Results:** Of the total 130 bacterial isolates Pseudomonas aeruginosa was the predominant isolate 32 (24.61%) followed by E. coli 27 (20%), K. pneumonia and S. aureus, 18.46% each. Gram negative bacilli were found to be commonest cause of ICU infection. ESBL production was found in 35.71% of Enterobacteriaceae isolates. **Conclusion:** ESBL producing organisms pose a major problem for clinical therapeutics. Judicious use of antimicrobials, strict adherence to the antibiotic policy and infection control practices, implementation and practice of antibiotic stewardship programme are measures to reduce infections in ICU.

Key words- Nosocomial infections, AMR, ESBL,

Introduction

A nosocomial infection - also called hospital acquired infection (HAI) or Health care associated infections (HCAI) can be defined as: An infection acquired in hospital by a patient who was admitted for a reason other than that infection. An infection occurring, in a patient, in a hospital or other health care facility, in whom, the infection was not present or incubating at the time of admission. This includes infections acquired in the hospital but appearing after discharge, and occupational infections among staff of the facility[1].

Infections play vital role in determining the outcome as well as cost and duration of the hospital stay for patients admitted in Intensive Care Unit (ICU) setup. One of the major problems Worldwide is the rise in Antibiotic-Resistant Strains of bacteria, mainly in hospitals[2]. The organisms that cause nosocomial infections have changed over the years because of selective pressures from the use, misuse, and overuse of antibiotics. Risk factors for the acquisition of highly resistant organisms include prolonged hospitalization and prior treatment with antibiotics[3]. The clinical isolates such as P. aeruginosa, MRSA, Enterococci especially VRE, and members of family Enterobacteriaceae, for example, K. pneumoniae, E. coli, and Proteus spp, rapidly develop antibiotic resistance and spread in the hospital environment[2].

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Infections frequently encountered with drug resistant organisms include those with Methicillin Resistance Staphylococcus aureus (MRSA), Extended-Spectrum β-Lactamase (ESBL), and Metallo β-Lactamase (MBL) producing organisms[4].

Extended-spectrum β-lactamase (ESBL) producing strains of Enterobacteriaceae have emerged as a challenge in hospitalized patients as well as in the community[2].

ESBLs are mutant plasmid mediated lactamase capable of conferring bacterial resistance to the penicillin first-, second-, and third-generation cephalosporins, and aztreonam (but not the cephamycins or carbapenems) by hydrolysis of these antibiotics, and which are inhibited by - β lactamase inhibitors such as clavulanic acid[5]. Because of their greatly extended substrate range, these enzymes were called as ESBL[6].

Thus, antibiotic resistance is major concern across the World, including India, thus, Surveys of the prevalence and susceptibility patterns of bacterial isolates are influential for optimum empirical therapy of infections in critically ill patients. In such situations, microbiologists play an important role for prevention and treatment of nosocomial infections caused by MDR organisms[4]. The present study was therefore planned with an objective to evaluate the antimicrobial susceptibility of prevalent gram negative organisms in ICU.

Objectives

1. To isolate and identify bacterial pathogens in Adult Intensive Care Unit (ICU)
2. To study antimicrobial susceptibility patterns of gram negative organisms isolated from samples in Adult ICU
3. To detect presence of Extended Spectrum β Lactamases in all Enterobacteriaceae isolates.

Material and methods

The study was carried out in Department of Microbiology at a Medical College Hospital, from December 2015 to May 2017. The hospital has 18 bedded adult ICU. The adult ICU provides care for both ventilated and non-ventilated patients and a mix of medical and surgical patients. The study was initiated after obtaining approval from the Institutional Ethical Committee.

Selection of cases

Inclusion Criteria

All patients admitted in adult ICU, with infection/s conforming to CDC guidelines were included in the study[7].

Exclusion Criteria

Patients admitted in adult ICU, with infection/s not conforming to CDC guidelines were excluded from the study[7].

The data of patients regarding age, sex, registration number, date of specimen collection, brief clinical history, associated co-morbid condition were recorded. Depending on sites of infections various samples were collected and processed as per the standard guidelines[8].

Specimens collected

Blood in bacteremia/septicaemia; Urine in urinary tract infection (UTI); Sputum, endotracheal tube aspirate, tracheostomy tube aspirate in pneumonia; purulent discharge, drain fluid, wound swab in surgical site infection (SSTI) and various body fluids like CSF, ascitic fluid, pleural fluid etc.

Antimicrobial susceptibility of all bacterial isolates was done. Each isolate was subjected to antimicrobial susceptibility test as per CLSI 2015 guidelines by Kirby-Bauer disk diffusion technique [9].

Statistical analysis

As the data is qualitative, Pearson's chi-square (x2) test of significance at 0.05 level is used wherever necessary. Statistical software Open Epi version 3.01(2013) was used for statistical analysis. Value of $p \leq 0.05$ was considered significant.

Results

In this Hospital based cross sectional study carried out in Department of Microbiology Government Medical College and Hospital, Akola 380 samples were collected from 343 patients admitted in ICU suspected of having nosocomial infection as per CDC guidelines during the period December 2015 to May 2017. Among the 343 patient whose samples were collected 123 were found to be infected and the infection rate was 35.86% in present study. Out of 343 study participants more than half ie. 205 (59.11%) were males, while 138 (40.23%) were females. Infection rate among males 37.56 % was more as compared to females 33.33%.The difference is not significant statistically. Out of 380 samples 130 (34.21 %) were found to be culture positive, while 250 (65.79 %) samples showed no growth.

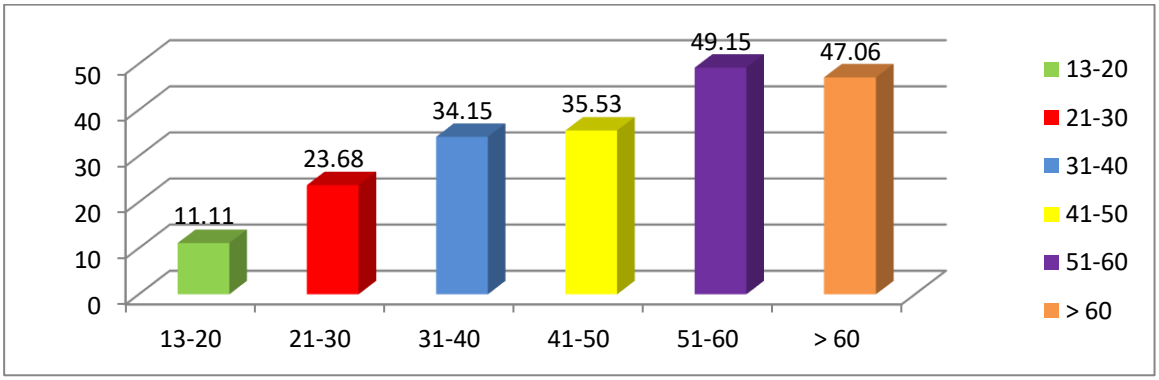

Fig 1: Showing Age-wise Culture Positivity

The above fig 1 shows that out of 380 total samples collected, the highest positivity (49.15%) was seen in 51-60 years age group. There is steady increase in sample positivity as the age increases

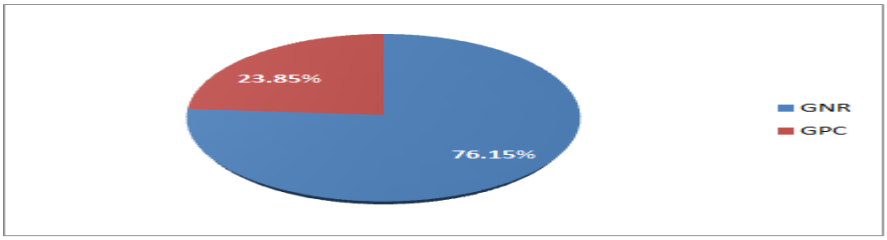

Fig 2: Organism-wise Distribution of Culture Positive Isolates

The fig 2 shows that in 130 total pathogens isolated Gram-negative were the main etiologic agents (76.15%) of the isolates, whereas gram positive accounted for a total of 31(23.85%).

Table 1: Bacteriological Isolates in Culture Positive Samples

Type of isolates	Number	Percentage%
1) Gram Positive	31	23.85%
Staphylococcus aureus	24 (MRSA=9)	18.46% (MRSA=37.5%)
Coagulase negative Staphylococcus (CONS)	2	1.54%
Enterococci spp	5	3.85%
2) Gram Negative	99	76.15%

Pseudomonas aeruginosa	32	24.61%
E. coli	26	20%
Klebsiella pneumonia	24	18.46%
Acinetobacter baumannii	11	8.46%
Proteus spp	6	4.62 %
Total isolates	130	100%

Of the total 130 bacterial isolates Pseudomonas aeruginosa was the predominant isolate 32 (24.61%) followed by E. coli 27 (20%), K. pneumonia and S. aureus, 18.46% each.

Table 2: Antimicrobial Resistance Pattern of Enterobacteriaceae

SN	Drugs	E. coli (N=26,100%)	K. pneumoniae (N=24,100%)	Proteus spp (N=6,100%)
1.	Ampicillin	20 (76.93)	20 (83.34)	5 (83.34)
2.	Amoxiclav	17 (65.38)	17 (70.83)	4 (66.67)
3.	Aztreonam	16 (61.54)	15 (62.5)	4 (66.67)
4.	Amikacin	8 (30.77)	6 (25)	1 (16.67)
5.	Ceftazidime	18 (69.23)	16(66.67)	4 (66.67)
6.	Cefotaxime	18 (69.23)	18 (75)	4 (66.67)
7.	Cefuroxime	19 (73.08)	19 (79.17)	5 (83.34)
8.	Cefepime	16 (61.54)	16 (66.67)	3 (50)
9.	Ciprofloxacin	13 (50)	10 (41.67)	2 (33.33)
10.	Gentamicin	11 (42.31)	9 (37.5)	1 (16.67)
11.	Pipercillin-tazobactum	9 (34.62)	12 (50)	2 (33.33)
12.	Imipenem	4 (15.38)	5 (20.83)	0 (0)
13.	Nitrofurantoin*	6/16 (37.5)	1/3 (33.33)	2/6 (33.37)
14.	Norfloxacin*	8 /16(50)	1/3 (33.33)	4/6 (66.67)

*Urinary antibiotics tested in urinary isolates

E.coli is found highly resistant to 3rd generation cephalosporins (cefotaxime and ceftazidime 69.23 % each) followed by ampicillin 76.93 % and amoxiclav 65.38%. Least resistance was seen in imipenem 15.38 %. K. pneumoniae is also found to have least resistance to imipenem 20.83% but more as compared to E.coli 15.38%. However, resistant to 3rd generation cephalosporin is found to be high ceftazidime 66.67% and cefotaxime 75%.. This study indicates low resistance in non-beta lactam antibiotics like aminoglycosides and carbapenems. Proteus spp were 100% sensitive to imipenem. This study indicates low resistance in non-beta lactam antibiotics like aminoglycosides and carbapenems. Urinary isolates showed variable resistance overall norfloxacin was found to be more resistant.

Table 3: Antimicrobial Resistance Pattern of Non-Fermenters

SN	Antibiotics	P. aeruginosa n=32	Acinetobacter spp n= 11
1.	Amikacin	12 (37.5)	6 (54.55)
2.	Aztreonam	20 (62.5)	-
3.	Ampicillin/Salbactum	-	5 (45.46)
4.	Ceftazidime	23 (71.88)	10 (90.91)
5.	Cefotaxime	-	10 (90.91)
6.	Cefepime	20 (62.5)	9 (81.82)
7.	Ciprofloxacin	23 (71.88)	9 (81.82)
8.	Gentamicin	15 (46.88)	8 (72.73)
9.	Pipercillin	16 (50)	7 (63.64)
10.	Pipercillin-tazobactum	9 (28.12)	6 (54.55)
11.	Imipenem	5 (15.63)	5 (36.37)
12.	Polymyxin B	0 (0)	-
13.	Tetracycline	-	9 (81.82)
15.	Norfloxacin*	1 (100)	-

*Tested for urinary isolates only

Table 3 shows antimicrobial resistance pattern of P. aeruginosa and Acinetobacter isolates In P. aeruginosa isolates high resistance was observed for cephalosporines, antipseudomonal penicillins, quinolones and monobactums. Among aminoglycosides resistance was less for amikacin 37.5%. Resistance to Pipercillin-tazobactum was 28.12% and for imipenem it was 15.63%. None of the isolates was resistant to polymyxin B.

In Acinetobacter spp high resistance was noted for commonly used antibiotics like cephalosporines, quinolones and aminoglycosides. Resistance to β -lactam / β -lactamase inhibitor combination was high. Resistance to imipenem was 36.37%.

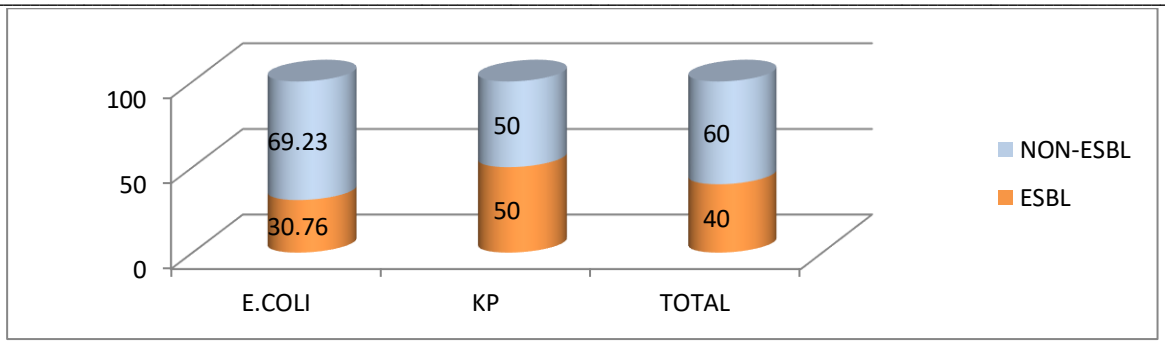

Fig 3: Showing ESBL Producing Isolates of E. coli and K. pneumoniae

Out of total 26 E. coli isolates 8 (30.76%) were found to be ESBL producers whereas ESBL production was reported up to 12 (50%) in the K. pneumoniae isolates. The statistical difference is not significant.

Discussion

The infection rate was 35.86% in the present study. Similar findings were noted by Pattanayak, et al [10] and Ghanshani, et al [11] where infection rate was 28.2% and 28%, respectively. In a study conducted at Chennai by Ravi, et al [12] 25% patients had a positive bacteriological culture.

In present study, out of 343 patients 205 (59.77%) were males, while 138 (40.23%) were females. The infection rate was 37.56% in males and 33.33% in females. Raval, et al [13] also reported higher infection rate among males

Table 4:Bacteriological culture positivity

SR.NO.	Study	Bacteriological culture positivity
1	**Present study**	**34.21%**
2	Patel, et al [4]	**41.02%**
3	Pattnayak, et al [10]	**58.3%**
4	Mehta, et al [14]	**48.78%**
5	Sarvepalli & Dharna [15]	**51.9%**

Age wise distribution of culture positivity: (Fig1)

The highest positivity (49.15%) was seen in 51-60 years age group followed by > 60 years (47.06%) whereas the lowest (11.11%) was reported in younger age group 13-20 years. Mean age of the study population was found to be 41.49%. Steady increase in sample positivity is observed as the age increases. The difference is statistically significant. Increase positivity in older age group seen can correlate with debilitating condition and diminishing immune status seen in this age group.

Organism wise distribution [Fig 2]

Infections due to Gram negative bacteria are becoming a great problem in health care facilities and ICU's.

Out of 130 total pathogens isolated in the present study Gram-negative organisms (GN) were the main etiologic agents for various infections in three-fourth (76.15%) of the isolates, whereas, Gram-positive (GP) accounted for a total of 31 (23.84%). Patel, et al [4] reported that 79.03% of infections were due to Gram-negative organisms. Similar findings were noted by Sudhamani, et al, [16] Ghanshani, et al, [11] and Raval et al [13] where Gram-negative organisms were predominant accounting 79%, 76%, 86.5%, respectively. . Indicap study [17] also reported that Gram-negative organisms to be 68.9%. Thus, studies in India indicate that Gram-negative organisms are still the predominant etiologic agent for infections in ICU's. Gram-negative organisms predominate in India and Asia-Pacific region, particularly those producing, Extended Spectrum Beta-Lactamases (ESBLs), AmpCs, and/or Carbapenemases. There is variations in prevalence within the country too, i.e., state to state, urban versus rural, health care versus community, government versus corporate/private hospitals, primary, secondary, and tertiary care hospitals. Local variations occur within a locality, community, different hospitals of a city, different wards of a hospital (ICU vs. general wards; and different ICUs such as surgical ICU, cardiac ICU, medical ICU, neonatal ICU, etc.) have different infections or microbes[18].

Bacteriological isolates in culture positive samples [Table 1]

The microbiology profile of the HAIs in the ICUs often reveals MDR ESKAPE pathogens (Enterococcus faecium, S. aureus including MRSA, K. pneumoniae, A. baumannii, P. aeruginosa and Enterobacter species).[20] The present study revealed that P. aeruginosa (24.61%) is commonest pathogen followed by E. coli (20%), K. pneumoniae (18.46%), S. aureus (18.46%), A. baumannii (8.46%), Proteus spp (4.62%), Enterococci spp (3.85%), and CONS (1.54%). Study by Singh et al ,[20] Raval, et al [13] Dasgupta, et al [21] also reported P. aeruginosa as the most common isolate accounting for 38.17%, 27.62%, and 32.5%, respectively.

Antimicrobial Resistance Pattern of E. coli [Table 2]

E. coli was found to be highly resistant to third generation cephalosporins (cefotaxime and ceftazidime, 69.23% each). Resistance to ampicillin was 76.93% and it was 65.38% to amoxiclav. Least resistance was seen to imipenem (15.38%). Patel, et al [4] reported nearly 80% of resistance to cephalosporins in agreement with the present study. In present study 30.77% of E. coli isolates were ESBL producers. Cefepime resistance was found in 61.54% of E. coli isolates, findings being in concordance with Patel, et al [4], where they found 72.5% resistance. On the contrary Singh, et al [20] reported 51.09% resistance for cefepime. Aminoglycosides were found to be second best treatment options; Carbapenems being the first in the present study. Resistance to amikacin and gentamicin was 30.77% and 42.31%, respectively. Singh, et al [20] reported resistance to aminoglycosides; amikacin (47.8%) and gentamicin (41.9%) similar to the present study. High resistance to amikacin (77.5%) and gentamicin (85%) was reported by Patel, et al[4].

Resistance to piperacillin-tazobactam was found to be 34.62% in the present study. Patel, et al [4] also found similar results with resistance of 37.5%. Imipenem resistance in the present study was 15.38%, which was higher than the study by Raval, et al[13].

Antimicrobial Resistance Pattern of K. Pneumoniae [Table 2]

Overall, K. pneumoniae isolates are found to be more resistant than other Enterobacteriaceae isolates in the present study. In the present

study, K. pneumoniae is also found to have least resistance to imipenem at 20.83%, but it is more as compared to E. coli (15.38%).
Resistance to third generation cephalosporins was (cefotaxime 75% and ceftazidime 66.67%). Cefepime resistance was 66.67%. Resistance to amikacin was found in 25% of the isolates. Singh et al [20] also reported findings in accordance to the present study. K. pneumoniae showed resistance to amikacin and gentamicin to be 30.77% and 42.31%, respectively in the present study. Patel, et al [4] reported 56.82% and 72.27% resistance to amikacin and gentamicin, respectively. Singh, et al [20] reported a resistance of 29.4% to amikacin which is similar to the current study.
In the present study, 50% of K. pneumoniae isolates were found resistant to Piperacillin-tazobactam whereas in study of Sudhamani, et al [16] and Sarvepalli, et al [15] it was 51.4% and10.3% respectively. Imipenem resistance in the present study was 20.83%. Sarvepalli & Dharana [15] also had findings in concordance with the present study with reported resistance to imipenem of 16.6%. On the contrary, Mehta, et al [14] and Ghanshani, et al [11] reported it to be as high as 55% and 58.3%, respectively.
This study indicates low resistance to non-β-lactam antibiotics like aminoglycosides and carbapenems. Urinary isolates showed variable resistance overall norfloxacin was found to be more resistant as compared to nitrofurantoin. Reistance for norfloxacin by E. coli, K. pneumonia and Proteus spp was found to be 50%, 33.33% and 66.67 % respectively in present study

Antimicrobial resistance pattern of P. aeruginosa isolates [Table 3]

In the present study, resistance to piperacillin and piperacillin-tazobactam was 50% and 28.12%, respectively. Patel, et al [4] reported 74.14% and 50% resistance to piperacillin and piperacillin-tazobactam, respectively. Raval, et al [13] and Sarvepalli, et al [15] found resistance of 16.99% and 8.2%, respectively for piperacillin-tazobactam, which is less as compared to the present study.
In the present study, among aminoglycosides, resistance to gentamicin and amikacin was 46.88% and 37.5%, respectively. Singh, et al [20] reported 60.38% and 33.16% resistance for gentamicin and amikacin, respectively. Patel, et al [4] obtained a high resistance to aminoglycosides, 87.93% and 74.13% for gentamicin and amikacin, respectively.
P. aeruginosa showed 15.63%, resistance to imipenem in the present study. Similar findings were reported by Patel, et al [4], Sarvepalli & Dharana [15] and Raval, et al [13] 13.79%, 18.4%, and 10.46%, respectively. High resistance to imipenem was reported by Mehta et al [14] (40.3%).

Antimicrobial resistance pattern of Acinetobactor spp [Table 3]

In the present study resistance of Acinetobactor spp to cephalosporines like cefotaxime, ceftazidime, and cefepime was 90.91%, 90.91%, and 81.82%, respectively. Raval, et al [13] and Patel, et al [4] found resistance to cefotaxime and cefepime to be 87.65%, 93.48% and 76.54%, 89.13%, respectively.
Resistance to pipercillin-tazobactum and amoxicillin-salbactum was 54.55% and 45.46%, respectively in the present study. Patel, et al,[4] Raval, et al,[13] and Sarvepalli, et al [15] reported 71.74%, 20.98%, and 12% of resistance to pipercillin-tazobactum, respectively. Resistance to amoxicillin-salbactum was reported by Patel, et al [4]was 32.61% while, it was 52.42% as reported by Raval, et al[13]. Among aminoglycosides resistance to gentamicin and amikacin was 72.73% and 54.55%, respectively in the present study. Raval, et al[13] reported resistance of 53.09% and 77.7% to amikacin and gentamicin, respectively, similar to the present study.

Table 5:ESBL production in Enterobacteriaceae isolates

SR.NO	STUDY	ESBL in Enterobacteriaceae isolate
1	Present study	35.17%
2	Sudhamani [16]	30%
3	Patel et al [4]	39.13%
4	Shanthi & Sekar [22]	67.32%.

None of the isolate of Proteus spp was found to be ESBL producer. Out of the 130 isolates, 26 (20%) were E. coli of these 8/26 (30.77%) were ESBL producers. Gopalkrishnan & Sureshkumar, [23] Shanthi & Sekar [22] and Ravi, et al [12] reported ESBL producing E. coli to be 65%, 72.05 and 49%, respectively, which is significantly higher than the present study. Basavaraj, et al [6] in their study found 31.7%, of the E. coli isolates, to be ESBL producers, which is similar to the present study.
The prevalence of ESBL producing isolates of K. pneumoniae was 50% in the present study (12/24). As observed by Sudhamani, et al [16] the prevalence of ESBL strains of K. pneumoniae was found to be 40.5% in their study. Gopalkrishnan & Sureshkumar [23] and Shanthi & Sekar [22], Basavaraj, et al [6] reported it to be 40%, 27.94% and 46.4%, respectively. The predilection of ESBL producing K. pneumoniae strains in the hospital environment is probably due to their longer survival in the hospital, thus facilitating cross infection[24]. Prevalence of ESBL production in K. pneumoniae isolates is more as compared to E. coli in the present study, however, the difference is statistically not significant.Detection of high percentage of ESBL producing strain in the present study may be due to over reliance on third generation cephalosporins to treat infections caused by Gram-negative organisms and lack of regulated hospital antibiotic policy in our Country.

Conclusion

Gram negative bacilli were found to be commonest cause of ICU infection. The most effective antibiotic for Gram-negative isolates was imipenem. Most of the organisms had good sensitivity to amikacin and piperacillin-tazobactam. It is therefore necessary to generate hospital data on antimicrobial sensitivity of common isolates, provide timely sensitivity report and provide advise regarding judicious use of antibiotics. ESBL production was found in 35.71% of Enterobacteriaceae isolates. ESBL producing organisms pose a major problem for clinical therapeutics. The incidence of ESBL producing strains among clinical isolates has been steadily increasing over the past few years resulting in limitation of therapeutic options. The routine susceptibility tests done by clinical laboratories fail to detect ESBL production. Routine testing of isolates for ESBL production is therefore necessary. Routine ESBL detection should be made imperative and empirical use of third generation cephalosporins must be discouraged.
Data on ICU infections collected prospectively gives an idea of success or failure of infection control programs. Keeping a track of ICU infections is important for outbreak surveillance, which is common in ICUs and early detection is vital. Appropriate and effective microbiological surveillance practices should be practised in for prevention of infections in ICU. The micro-organisms that cause infections in one part may not be the same in other parts. Pattern and prevalence of bacterial isolates in ICU tends to change with time. Thus, local data is required to help to formulate antibiotic policies and thereby prevent any emerging outbreak early before, it leads to serious consequences.Judicious use of antimicrobials, strict adherence to the antibiotic policy and infection control practices, implementation and practice of antibiotic stewardship programme are measures to reduce infections in ICU.

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