PREVALENCE OF CARBAPENEM RESISTANT ENTEROBACTERIACEAE- A STUDY IN A TERTIARY CARE HOSPITAL IN MUMBAI

Sukanya Verma¹, Suyasha S. Thorat², Kishore Bisure³

¹Speciality Medical Consultant, Department of Microbiology, Group of TB Hospital, Sewree, Mumbai, Maharashtra, India.

²Assistant Professor, Department of Microbiology, HBTMC and Dr. R. N. Cooper Hospital, Juhu, Mumbai, Maharashtra, India.

³HOD, Department of Microbiology, HBTMC and Dr. R. N. Cooper Hospital, Juhu, Mumbai, Maharashtra, India.

ABSTRACT

BACKGROUND

The global incidence of carbapenem resistant organisms is on the rise and can be attributed to indiscriminate use of carbapenem to tackle the Extended Spectrum Beta Lactamase (ESBL) producing organisms. Carbapenem resistance is associated with resistance to other group of antibiotics. The spread of resistance from one bug to another is not uncommon. The organism persists in the hospital environment and is identified as cause of hospital-acquired infections. This is not only a major concern in the healthcare setting but is also increasingly being recovered from community settings also. Limited availability of drugs to treat these infections is the biggest concern. Identifying carbapenem resistant organisms and implementing measures to prevent the spread is need of the hour.

The aim of this study is to determine the prevalence and susceptibility pattern of Carbapenem resistant Enterobacteriaceae.

MATERIALS AND METHODS

A descriptive study was carried out in the Department of Microbiology of a tertiary care teaching institute of Mumbai. All Enterobacteriaceae isolates recovered during the six months study period of January 2017 to June 2017 were included in the study. The isolates were identified using standard conventional biochemical methods. Antimicrobial susceptibility was performed using the Kirby-Bauer disc diffusion technique and interpreted as per CLSI 2016 standards.

RESULTS

A total of 442 isolates of Enterobacteriaceae were recovered during the study period. The different strains isolated included *Escherichia coli* (218), *Klebsiella pneumoniae* (161), *Proteus* spp. (42), *Salmonella* (9), *Citrobacter* spp. (1) and *Enterobacter* spp. (1); 107 out of 442 (24.2%) were Carbapenem resistant 18.8% of *E. coli*, 37.9% of *Klebsiella pneumoniae*. Maximum number of CRE were recovered from Medicine Department (34.1%). The least number of CRE isolates were recovered from ENT (5.8%).

CONCLUSION

The prevalence of Carbapenem resistant isolates is high in our settings. Strict adherence to infection control practices and stringent implementation of antimicrobial stewardship is essential to curb the rate of Carbapenem resistant isolates.

KEY WORDS

Enterobacteriaceae, Carbapenem Resistant, Antimicrobial Stewardship, Infection Control.

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BACKGROUND

A rise in incidence of carbapenem resistance among Enterobacteriaceae has been observed recently.^{(1),(2)} This rise can be attributed to increase in number of Expanded Spectrum Beta Lactamase producing organisms (ESBL). The drug of choice for these ESBL producing isolate is carbapenem. Use of carbapenem to tackle the problem of ESBL producing strains has led to indiscriminate use of carbapenem, which has ultimately resulted in developing resistance to these carbapenems.^{(3),(4)} The other factors that may be responsible for increased incidence of CRE are the use of carbapenem in animals, their relative action and utilisation

in the gut microbiota, poor isolation and infection control practices in different health care settings and increased trend of travel. Carbapenem group of drug comprises of ertapenem, imipenem, meropenem and doripenem. Resistance to carbapenem is mediated either by production of enzyme carbapenemases which are capable of hydrolysing all penicillins, cephalosporins, monobactams and carbapenem. The other mechanism of development of carbapenem resistance is poor binding of carbapenem to penicillin binding protein accompanied by overexpression of efflux pumps and overproduction of expanded spectrum beta lactamases coupled with porin loss.⁽⁵⁾

The resistance to carbapenem is plasmid mediated and gene responsible for carbapenemase production are found on transposons and can easily be transferred horizontally to other Enterobacteriaceae and Non-Enterobacteriaceae like *Pseudomonas* spp. and *Acinetobacter* spp. thus posing an increased risk of spread of resistance among susceptible isolates.⁽⁶⁾ Carbapenem resistance is also associated with resistance to other antibiotic group of agents like fluoroquinolones and aminoglycosides, since the genes for resistance to these agents may be present on the same plasmid.⁽⁶⁾

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Corresponding Author:

Dr. Sukanya Verma,

Speciality Medical Consultant,

Group of TB Hospital,

Jerbai Wadia Road, Sewree, Mumbai,

Maharashtra, India.

E-mail: drvermasukanya@gmail.com

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Increasing resistance can pose a serious threat to the health care, since these agents are one of the last resorts for treatment of multidrug resistant isolates.^{(5),(3)} The emergence of carbapenem resistance is directly associated with raised morbidity and mortality upto 40 to 50% in some studies.^{(7),(8)}

Though, the prevalence of multi-drug resistant organism varies from country, institution and area, the prevalence of Carbapenem resistant Enterobacteriaceae (CRE) in India ranges from 13 - 51%.^{(1),(2)}

Over the period of time, as more data is being collated, it is observed that these organisms are mainly isolated from the health care workers and also transmitted within. Therefore, methodologies and strategies to minimise the risk of transmissions in this group are being devised.⁽⁷⁾

With this background, this study was carried out to screen for the presence of Carbapenem resistant Enterobacteriaceae in our institute.

MATERIALS AND METHODS

A descriptive study was carried out in the Department of Microbiology of a tertiary care hospital of Mumbai.

The gram-negative isolates belonging to family Enterobacteriaceae that were recovered during the period of six months, i.e. from January 2017 to June 2017 were included in the study. The isolates were obtained from various clinical specimens like sputum, urine, pus and blood. The isolates were separated based on the place of isolation into outpatient and inpatient.

The isolates were identified using standard conventional biochemical testing methods. (Ref: Manual of Clinical Microbiology). After identification, the isolates were subjected to antimicrobial susceptibility testing using Kirby-Bauer disc diffusion testing. Screening for carbapenem resistance was done using meropenem (10 µg) and imipenem (10 µg) disc by Disc diffusion testing. The antibiotic discs were procured from Hi-Media. The zone diameters were interpreted as per CLSI 2016.

The zone diameters for Imipenem and Meropenem, if ≥ 16 mm were considered to be sensitive, if ≤ 13 mm were resistant and 14 mm were intermediate (which were considered as resistant for final data analysis). E. coli ATCC 25922 was used as control for the Kirby-Bauer disc diffusion method.

As per CDC 2012 toolkit all isolates non-susceptible to imipenem, meropenem or doripenem and resistant to all third-generation cephalosporins tested were considered to be Carbapenem resistant Enterobacteriaceae (CRE).⁽⁹⁾

Later the definition was modified for surveillance purpose, so as to include Enterobacteriaceae that test as resistant to any of the carbapenem agents or evident production of carbapenemase detected by any phenotypic or molecular assay.⁽⁸⁾

RESULTS

A total of 442 gram-negative bacilli belonging to family Enterobacteriaceae were isolated during the study period. These isolates were recovered from various specimen that included pus, urine, blood and sputum.

Of the total 442 isolates, 273 isolates were recovered from inpatient department and 169 were recovered from outpatient department.

The different strains of gram-negative bacteria isolates included Escherichia coli (218), Klebsiella pneumoniae (161),

Proteus spp. (42), Salmonella (9), Citrobacter spp. (1) and Enterobacter (1). 107 strains out of 442 were resistant to carbapenems (24.2%).

Species	CRE	Total	Percentage
Escherichia coli	41	218	18.8
Klebsiella pneumoniae	61	161	37.9
Proteus spp.	4	42	9.5
Salmonella spp.	0	9	0
Citrobacter spp.	1	11	9
Enterobacter spp.	0	1	0
Total	107	442	24.2

Table 1. Species Wise distribution of Carbapenem Resistant Strains

18.8 % of E. coli, 37.9% of Klebsiella pneumoniae, 9.5% of Proteus spp. and 9% of Enterobacter spp. were resistant to carbapenem.

Specimen	CRE	Total	Percentage
Sputum	11	50	10.5
Pus	59	211	27.96
Urine	34	156	21.8
Blood	3	25	12
Total	107	442	24.2

Table 2. Specimen wise distribution of Carbapenem Resistant Strains

27.96% of isolates were recovered from pus, 10.5% isolates from sputum, 21.8% from urine and 12% from blood were carbapenem resistant.

	Inpatient			Outpatient			Total (CRE)	%
	CRE	Total	%	CRE	Total	%		
Medicine	37	89	41.5	7	40	17.5	44/129	34.1
Surgery	32	95	33.6	3	28	10.1	35/123	28.4
Paediatrics	10	43	23.25	1	24	4.1	11/67	16.41
OBGY	7	30	23.33	3	57	5.2	10/87	11.49
ENT	0	0	0	1	17	5.8	1/17	5.8
Orthopaedics	5	16	31.25	1	3	33	6/19	31.5
Total	91	273	33.33	16	169	9.4	107/242	

Table 3. Department Wise distribution of Isolates and Carbapenem Resistance

33.33% and 9.4% of isolates from inpatient and outpatient isolates were carbapenem resistant respectively. Maximum number of CRE were recovered from Medicine (34.1%) followed by Orthopaedic (31.5%), Surgery (28.4%), Paediatrics (16.41%) and OBGY (11.49%). The least number of CRE isolates were recovered from ENT (5.8%).

	Sensitive	Intermediate	Resistant	Total
Imipenem	22	5	80	107
Meropenem	8	3	96	107

Table 4. Pattern of CRE

Out of 107 CRE, 80 isolates were resistant to imipenem, 96 isolates were resistant to meropenem. 77 out of the 107 were resistant to both imipenem as well as meropenem.

5 and 3 isolates were intermediate to imipenem and meropenem respectively were included under resistant for further analysis.

DISCUSSION

Increase in the indiscriminate use of antibiotics has led to emergence of multi-drug resistant strains. Limited treatment options are available for treating these multi-drug resistant strains. Most of the organisms carry drug resistant gene on transposon, which can easily spread from one organism to other.

Development of resistance to carbapenem is one of the burning issues that needs immediate attention and action for prevention of spread. There are various methods described by CLSI for detection of carbapenem resistance.⁽¹⁰⁾ Screening for carbapenem resistance can be done using Meropenem (10µg) or Ertapenem (10 µg) disc. Ertapenem is considered to be more sensitive followed by meropenem and imipenem.^{(8),(11)} In our study, meropenem (10 µg) and imipenem disc (10 µg) were used for screening of carbapenem resistance.

The other methods recommended by CLSI for confirmation of carbapenem resistance include Modified-Hodge test, Carba NP (for detection of enzyme Carbapenemases), mCIM and molecular assay.⁽¹⁰⁾

Of the 442 isolates of Enterobacteriaceae recovered in our study, 107 were resistant to either one or both imipenem and meropenem. Thus, the prevalence of CRE based on this data in our study is 24.2%. The prevalence of CRE varies globally. The prevalence of CRE according to some institutions in epidemic area varies between 24.7% and 29.8%.⁽³⁾ In a study from Mumbai, Delhi and Chandigarh the prevalence was 12.26% and 71.25% and 7.87% respectively.^{(12),(13),(14)} The variation in prevalence of Carbapenem resistant Enterobacteriaceae from various institutions could be because of the different level of hospital infection control practises that were followed and the implementation of antimicrobial stewardship program.⁽¹⁴⁾ Few studies have also detected the CRE status by surveillance of stool. The results varied from 9% to 20% in different regions of India.^{(15),(16)}

In our study, the prevalence of Carbapenem resistance was found to be more in *Klebsiella pneumoniae* (61%) followed by *E. coli* (41%). This finding is supported by another study carried out by Tempe DK et al.^{(17),(18)} In another screening study carried out, the prevalence was 26% and 41% for *Klebsiella pneumoniae* and *E. coli* respectively.⁽⁵⁾ In studies carried out by Nagraj et al and Nair et al, the prevalence for *E. coli* was 60% and that for *Klebsiella pneumoniae* is 33%.^{(1),(12)}

In our study, resistance to carbapenem was also noticed in 9% of *Proteus* spp. and *Citrobacter* species. This is the correlation with other studies.⁽⁵⁾ None of the Enterobacter species showed Carbapenem resistance which is contrast with other studies.⁽⁵⁾

Carbapenem resistance in *Salmonella* species is not known, which is similar to the finding of our study.

Majority of the carbapenem resistant Enterobacteriaceae were isolated from the pus sample (27%) followed by urine (21%) sample. Other studies carried showed that CRE were more common in urine followed by pus.^{(5),(1),(12),(18)}

The other specimen from which CRE were isolated included sputum and blood, which was almost similar to that found in other studies.⁽¹⁸⁾

85% of the total isolates of CRE were isolated from various inpatients departments that included Medicine, Surgery,

Obstetrics and Gynaecology, Paediatric and Orthopaedics. 15% were isolated from Outpatient departments. Our study findings co-relates well with studies, which have also shown the same pattern.^{(19),(20)}

Admission to a hospital setting predisposes the patients to colonisation followed by infection with CRE, which is the reason for increased isolation of CRE from inpatient departments.⁽⁶⁾ Also, in the present study maximum number of isolates were recovered from the wards, which could be due to cross-transmission from one patient to another. This points out towards improving the need for implementation of various precautionary measure essential to prevent the spread of such resistant isolates. Maximum number of CRE isolates were from Medicine followed by Orthopaedics. The reason attributed to this could be use of increased usage of Carbapenem for treating invasive infections.

96 out of 107 CRE isolates were resistant to meropenem (22.39%). 80 out of 107 CRE were resistant to Imipenem (19.2%).

77 out of 107 were resistant to both imipenem and meropenem (17.4%).

Increased resistance to meropenem observed in our study could be due to excessive use of meropenem as compared to imipenem. Increased resistance to meropenem is supported by other studies, which also show a similar finding.⁽⁵⁾

Since treatment options available for carbapenem resistant isolates are very few which include tigecycline, colistin or combination therapy increasing resistance to Carbapenem is of rising concern.

Absence of proper antimicrobial policy at our institution could have resulted in indiscriminate use of carbapenem. It has resulted in overall increase in these group of drugs. Introduction of appropriate antimicrobial stewardship program may help curb the issue. Use of optimal dose for specified duration and use of combination antibiotics are some of the measures that may play an important role.⁽²¹⁾

CONCLUSION

The prevalence based on screening test for Carbapenem resistance is 24%. Implementation of infection control practices and proper antibiotic policy is the need of the hour to curb the rate of carbapenem resistant organism.

Limitation of the Study

The isolates in our study were screened for carbapenem resistance using disc diffusion as per CLSI. Determination of MIC that would ascertain the isolates as carbapenem resistant could not be performed due to cost constraints. Also, it could not be confirmed as to whether the isolates were resistant to carbapenem because of carbapenemases.

Main limitation of our study was that screening for carbapenem resistance was performed using meropenem and imipenem disc diffusion. However, Ertapenem which is more sensitive indicator for screening of carbapenem could not be used because of non-availability of the disc. Secondly, the confirmatory test for carbapenemase production and other confirmatory tests could not be performed because of cost-constraints.

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