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Prevalence of Carbapenem Resistant Enterobacteriaceae Isolated in Tertiary Care Hospital in NMC and Hospital, Nellore, Andhra Pradesh, India

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A B S T R A C T

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 central laboratory of Microbiology, tertiary care teaching institute of Narayana medical college and Hospital, Nellore, AP, India. All Enterobacteriaceae isolates recovered during the six months study period of August 2021 to January2022 were included in the study. The isolates were identified using vitek2. Antimicrobial susceptibility was performed using vitek2. Results: A total of 592 isolates of Enterobacteriaceae were recovered during the study period. The different samples included sputum158, urine 242, blood 56, pus 136. Out of which592 isolates, 126 are resistance (21.28%). The strains isolated includes *Escherichia coli*, *klebsiella pneumonia* and other speces (Proteus spp.,, Citrobacter sp, serracia). *Escherichia coli* (246), *Klebsiella pneumoniae* (177), other speces 169 (Proteus sp, Citrobacter sp, serratia). *Escherichia coli* strains 72(29.26%), *klebsiella pneumonia* strains 30(16.95%) others strains (Proteus spp., Citrobacter sp, serratia) 24(14.20%) are carbapenem resistant enterobacteriaceae (CRE). 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.

Introduction

A rise in incidence of carbapenem resistance among Enterobacteriaceae has been observed recently (Nagaraj *et al.,* 2012; Suwantarat and Carroll, 2016). 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 (Xu *et al.,* 2012; Nordmann *et al.,* 2011). The other factors that may be responsible for increased incidence of CRE are the use of carbapenem in animals, their relative action and utilization 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 carbapenemase 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 (Parimala, 2017).

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 (Perez and Van Duin, 2013). 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 (Perez and Van Duin, 2013).

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 (Parimala, 2017; Xu *et al.,* 2000-2012). The emergence of carbapenem resistance is directly associated with raised morbidity and mortality upto 40 to 50% in some studies (CDC, 2015; Lutgring and Limbago, 2016).

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% (Nagaraj *et al.,* 2012; Suwantarat and Carroll, 2016).

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 (CDC, 2015). 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 central laboratory of Microbiology, tertiary care hospital of Narayana Medical College and Hospital. Nellore, AP, India.

The gram-negative isolates belonging to family Enterobacteriaceae that were recovered during the period o six months, i.e. from August 2021 to January 2022 were included in the study. The isolates were obtained from various clinical specimens like sputum, urine, pus and blood.

The isolates were identified using vitek2 system. After identification, the isolates were subjected to antimicrobial susceptibility testing using vitek2 system. 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) (2012).

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 (Lutgring and Limbago, 2016).

Results and Discussion

A total of 592 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 592 entero bacteria isolates 158 isolates from sputum, 242 from urine, 56 from blood, 126 from pus respectively in sputum 158are isolated 40 are resistant (25.32%) in urine242 isolated 68 are resistant (28.10%), blood 56 isolated 4 are resistant (7.04%) in pus 136 isolated 14are resistant (10.29%) out of 592 isolate 126 are resistant (21.28) as shown in table.1.

The different strains of enterobacteria isolates included *Escherichia coli, Klebsiella pneumoniae* and others (*Proteus* spp., *Citrobacter* sp, *Serratia*). *Escherichia coli* 246 isolated 72 are resistant (29.26%), *Klebsiella pneumoniae* 177 are isolated 30 are resistant (16.95%), others (*Proteus* spp., *Citrobacter* sp, *Serratia*) 169 are isolated 24 are resistant (14.20%) with a total of 126 resistant (21.28%) as shown in table 2

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 (Lutgring and Limbago, 2016; CLSI, 2014).

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 (CLSI, 2017).

Of the 592 isolates of Enterobacteriaceae recovered in our study, 126 were resistant to either one or both imipenem and meropenem. Thus, the prevalence of CRE based on this data in our study is 21.28%. The prevalence of CRE varies globally.

Table.1 Specimen wise distribution of carbapenem resistant strains

Specimen	CRE	Total	Percentage
Sputum	40	158	**25.32**
Urine	68	242	**28.10**
Blood	4	56	**7.14**
Pus	14	136	**10.29**
Total	**126**	**592**	**21.28**

Table.2 Species wise distribution of carbapenem resistant strains

Species	CRE	Total	Percentage
Escherichia coli	72	246	**29.26**
Klebsiella pneumoniae	30	177	**16.95**
Others	24	169	**14.20**
Total	**126**	**592**	**21.28**

The prevalence of CRE according to some institutions in epidemic area varies between 24.7% and 29.8% (Xu *et al.*, 2012). In a study from Mumbai, Delhi and Chandigarh the prevalence was 12.26% and 71.25% and 7.87% respectively (Nair and Vaz, 2013; Kumar and Bahdauria, 2014; Datta *et al.*, 2012). 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 (Datta *et al.*, 2012).

Few studies have also detected the CRE status by surveillance of stool. The results varied from 9% to 20% in different regions of India (Thacker *et al.*, 2014; Rai *et al.*, 2014).

In the study, the prevalence of Carbapenem resistance was found to be more in *Esherichea coli* is 72 (29.26%) followed by *Klebsiella pneumoniae* 30 (16.95%) and others 24 (14.20%). In studies carried out by Nagraj *et al.*, (2012) and Nair and Vaz (2013) the prevalence for E. coli was 60% and that for *Klebsiella pneumoniae* is 33%. In the present study majority of the carbapenem resistant Enterobacteriaceae were isolated from the urine 242 sample (28.9%) followed by sputum 128 (25%), pus 136 (10.29%) blood sample is 56 (7.14%).

Other studies carried showed that CRE were more common in urine followed by pus122 (Parimala, 2017; Nagaraj *et al.*, 2012; Nair and Vaz, 2013 and Gunjal *et al.*, 2014).

The other specimen from which CRE were isolated included sputum and blood, which was almost similar to that found in other studies (Gunjal *et al.*, 2014). 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. (Parimala, 2017).

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. Ithas 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. (Bogan and Marchaim, 2013)

The prevalence based on screening test for Carbapenem resistance is 21.28%. 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

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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