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Research Article

LEADING TREND OF CARBAPENEM RESISTANCE IN ENTEROBACTERIACEAE IN INDIA

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ABSTRACT
Carbapenem Resistance in Enterobacteriaceae including *Klebsiella pneumoniae* carbapenemase (KPC), *E.coli* & some spp. of Enterobacter, are newly emerging antimicrobial-resistant bacteria that are difficult to treat and cause infections with high mortality rates. In this research studied the carbapenum resistance activity in Enterobacteriaceae from New Delhi. In this research CRE positive cases were founded to be increasing studied. Out of 80 cases 57 (71.25%) cases showed carbapenem resistance, showing a rise in proportion from 65% to 85 %. ICU patient's positivity was founded about 66%. The proportion of KPC-positive patients transferred from a long-term care facility or long-term acute care hospital have risen during both the consecutive months. Urine (37%), sputum (32%), blood (19.3%) and endotracheal secretions (3.5%) were the most common sites of CRE infection or colonization. From the CRE positive cases 86% were *Klebsiella pneumoniae (KPC- Klebsiella pneumoniae Carbapenem)*, 8.80% were *E.coli* isolates & 5.3% of *Enterobacter cloacae.* All these isolates were ESBL producing organisms and were found resistant to almost all drugs of cephalosporin subclass4 (Ceftriaxone, Ceftizozime, Ceftazidime, Cefotaxime, Cefoperazone), Cefepime, Cefoperazone-Sulbactam, Collistin, Aztreonam, Co-Trimoxazole and very few to Chloramphenicol, Tetracycline, Gentamicin and most were sensitive to Amikacin.

Keywords**:** *Klebsiella Pneumonia, Carbapenemase, Enterobacter Cloacae; Klebsiella Pneumonia, Cephalosporin.*

INTRODUCTION
Enterobacteriaceae is a family of gram-negative bacilli that found naturally in the gastro-intestinal tract. These organisms can increase outside the gastro-intestinal tract and cause serious infections such as bacteraemia, pneumonia, urinary tract and wound infections. Clinically vital genera include *Escherichia, Klebsiella, Enterobacter, Serratia*, *Citrobacter*, *Proteus* and *Morganella* (Patel *et al.,* 2008). *Klebsiella* is an important human pathogen that has been associated in recent decades with nosocomial outbreaks and primarily attack immune compromised individuals who are hospitalized and suffer from severe underlying diseases such as diabetes mellitus, chronic pulmonary obstruction, urinary tract infections, pneumonia and intra-abdominal infections (Carpenter, 1990). After the introduction of extended-spectrum cephalosporins, extended spectrum β-lactamase (ESBL)-producing *Klebsiella pneumoniae* have become an increasingly serious problem worldwide (Jacoby and Han, 1996). The carbapenem group of antibiotics are considered last resort antibiotics as they offer broad spectrum antibiotic cover, enabling secure and useful treatment for severe infections. Carbapenem-resistant *Enterobacteriaceae* (CRE) occur due to the acquisition of carbapenemase enzymes (i.e. carbapenemase-producing *Enterobacteriaceae* or CPE) or less commonly arise via other mechanisms (e.g. porin loss). Within the *Enterobacteriaceae* family, carbapenemases have been initiate most commonly in *Escherichia coli* and *Klebsiella pneumoniae*, although have also been reported in other genera of gram-negative bacteria, such as *Pseudomonas* and *Acinetobacter* species. Carbapenems were first introduced in 1980 and they are now frequently used as the last choice in treating serious infections caused by multidrug-resistant strains of Gram negative bacilli in intensive care units (ICUs) and in high risk wards. These are stable to β -lactamase including the ESBLs and AmpC produced by Gram negative bacilli (Rodloff *et al.,* 2006; Matsumoto *et al.,* 1996 Zhanel *et al.,* 2007).

NDM enzymes were first reported for *K. pneumoniae* as well *E. coli* strains recovered from a Swedish patient who had been hospitalized in New Delhi, India, previously (Yong *et al.*, 2009). Recent reports from the Indian subcontinent (including India, Pakistan, and Bangladesh) show that the distribution of NDM -lactamases among clinical and environmental isolates of Gram-negative bacteria is widespread in these countries (Castanheira *et al.*, 2011; Castanheira *et al.*, 2011; Lascols *et al.*, 2011; Walsh *et al.*, 2011). The majority of NDM-1- producing bacteria *E. coli* and *K. pneumoniae* are broadly resistant to various drugs (Nordmann *et al.*, 2011). In current paper studied the susceptibility patterns and commonest occurrence factors of New Delhi superbug (ndm1-New Delhi Metallo beta-lactamase-1). With it Antibiotic susceptibilities were determined by cross checking Vitek-2 and BD-Phoenix100 results with that of ESBL producing and carbapenemase resistant enterobacteriaceae suspected by manual sensitivity. These suspected cases of CRE were further also confirmed by Modified Hodge test.

MATERIALS AND METHODS

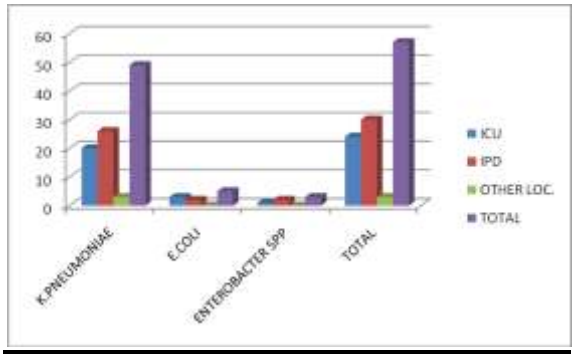
A total of 80 patients were selected for the study. In this study, 57 cultures were studied for their sensitivity patterns in vitek-2 or BD Phoenix-100. For it, carbapenemase cases included patients Suspected from all the units of Max, Saket i.e. IPD, ICU, OPD and triage in all over Delhi. The reoccurrence of resistance against Ertapenem and Meropenem in vitek-2 and BD Phoenix 100 sensitivity results leaded to confirmation towards carbapenem resistant Enterobacteriaceae. This sensitivity was further confirmed by performing a confirmatory test MODIFIED HODGE TEST, as per CLSI guidelines. The isolates giving positive results were analyzed to determine the trend of CRE, their susceptibility patterns, distribution of carbapenemase resistant samples.

Antibiotic sensitivity testing was performed on Mueller Hinton Agar plates with commercially available discs (Hi- Media, Mumbai) by Kirby-Bauer disc diffusion method. The results were recorded and interpreted as per the CLSI guidelines. ATCC25922 *E. coli* and ATCC *Klebsiella* were used as the standard controls to check antimicrobial disk potency by Kirby-Bauer method.

RESULTS AND DISCUSSION

Out of 80 cases 57 (71.25%) cases showed Carbapenemase resistance, showing a rise in proportion from 65% in December to 80 % in January & 85% in Feb. The proportion of KPC-positive patients transferred from a long-term care facility or long-term acute care hospital have risen during both the consecutive months. The first Metallo-B-Lactamase-producing *P. aeruginosa* strain was isolated in Japan in 1988 (Akke and Johann, 2012). For many years, these MBL producing isolates were restricted to Japan, but now it has disseminated worldwide (Watanabe *et al.*, 1991; Cornaglia *et al.*, 1999; Woodford *et al.*, 1998). Carbapenem resistance in *Klebsiella spp*. is an emerging problem and is a cause of concern as many nosocomial *Klebsiella spp*. are detected to be resistant to most other antibiotics. There is a limited literature available regarding the prevalence of resistance to carbapenems in *Klebsiella spp* from clinical isolates in our country. In Delhi, Gupta *et al.*, 2006 reported 6.9% of Meropenem resistance and 4.3% of Imipenem resistance in *Klebsiella* (Gupta *et al.*, 2006). Similarly in Kanpur reported no Carbapenem resistance among *K. pneumoniae* tested by Prakash, 2006. Praveen *et al.*, 2010 studied K. pneumoniae from 134 clinical isolates having about 43.6% percent isolates were resistant to Meropesnem, 32% to Imipenem, 20.3% to Ertapenem and 60% were resistant to Colistin. None of them were Metallo-beta-lactamases producers (Praveen *et al.*, 2010). In our study, Urine (37%), sputum (32%), blood (19.3%), Endotracheal secretions (3.5%) and were the most common sites of CRE infection or colonization. From the CRE positive cases 86% were *Klebsiella pneumoniae (KPC- Klebsiella pneumoniae Carbapenem)*, 8.8% were *E. coli* isolates & 5.3% of *Enterobactercloacae*. All these isolates were ESBL producing organisms and were found resistant to almost all drugs of cephalosporin sub class4 (Ceftriaxone, Ceftizozime, Ceftazidime, Cefotaxime, Cefoperazone), Cefepime, Cefoperazone-Sulbactam, Collistin, Aztreonam, Co-Trimoxazole and very few to Chloramphenicol and Tetracycline, Gentamicin and most were sensitive to Amikacin. Amikacin showed sensitivity in maximum.

Graph: 4.1 Occurrences of Different Organisms in Different Units of the Hospital



Graph: 4.2 Distribution of Carbapenemase Resistant *Enterobacteriacae* in Different Samples

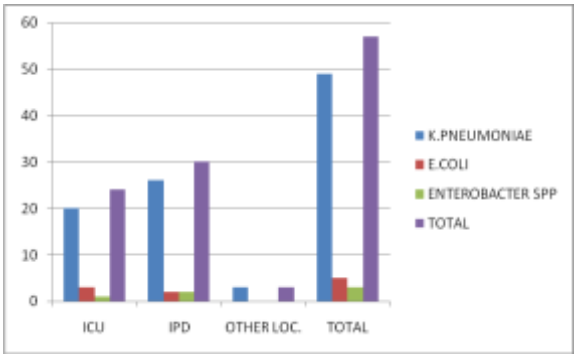


Table 1: Distribution of Carbapenemase Resistant *Enterobacteriacae* in ICU, IPD and Other Location

Organism	ICU	IPD	OTHER LOCATION	TOTAL
K. pneumonia	20	26	3	49
E. coli	3	2	0	5
Enterobacter spp.	1	2	0	3
Total	24	30	3	57

Table 2: Distribution of Carbapenemase Resistant *Enterobacteriacae* in Different Samples

	Urine	Sputum	Blood	Endotracheal secretion	Bal	Swab	Other fluids	Total
IPD	11	12	3	1	0	1	0	28
ICU	8	5	8	1	0	0	4	26
OPD	0	0	0	0	0	0	0	0
TRIAGE	0	0	0	0	0	0	0	0
OTHER LOC.	2	1	0	0	1	0	0	3
TOTAL	21	17	11	2	1	1	4	57

Conclusion

Klebsiella-pneumoniae Carbapenemase (KPC) is becoming the primary type of Carbapenemase responsible for CRE in New Delhi to date. The rise may be influenced in part by increased awareness, new screening protocols and enhanced laboratory methods for detection, history of taking certain antibiotics for long periods of time, invasive medical devices such as ventilators or intravenous catheters. Residents of long-term care (chronic medical conditions) may be a major reservoir and source of KPCs. Further studies are needed to determine risk factors for infection/colonization and to develop effective measures to prevent spread.

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