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## Research article

### PREVALENCE, CHARACTERIZATION AND CLINICAL SIGNIFICANCE OF *KLEBSIELLA PNEUMONIAE* CARBAPENEMASE (KPC) PRODUCING *KLEBSIELLA PNEUMONIAE*

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## ABSTRACT

**Background:** *Klebsiella pneumoniae*, a capsulated gram negative bacillus is responsible for causing life threatening infections in humans. Carbapenems are the drug of choice for serious infection caused by multidrug resistant *Klebsiella pneumoniae*. The emergence of carbapenem resistance has made it extremely difficult to treat such infections resulting in significant morbidity and mortality. **Aims:** To study the prevalence of carbapenem resistance using ertapenem as a marker and to detect *Klebsiella pneumoniae* Carbapenemase (KPC) producing *Klebsiella pneumoniae* as a mechanism of resistance. **Material and Methods:** The study included 102 patients from which *Klebsiella pneumoniae* isolated. Identification and antibiotic susceptibility testing of *Klebsiella pneumoniae* was performed on miniAPI (Analytical Profile Index, Semiautomated bacterial identification system) according to Clinical and Laboratory Standards Institute (CLSI) guidelines of 2011. The modified Hodge test was performed for detection of Carbapenemase production. Patient's clinical and demographic details along with risk factors and co-morbid conditions, type of response to antimicrobial therapy and mortality were collected. **Results:** The prevalence of carbapenem resistance was found to be 30.41% with 16.6% KPC producing *Klebsiella pneumoniae*. The co-morbid conditions like immunocompromised state ( $p = 0.042$ ), prior antibiotics therapy ( $p = 0.047$ ), previous hospitalization ( $p = 0.021$ ), intensive care unit stay ( $p = 0.047$ ) and use of indwelling devices ( $p = 0.013$ ) were found to be significantly associated with carbapenem resistance. Adverse clinical outcomes (death or worsening) among patients infected with ertapenem resistant patients was found to be statistically significant than ertapenem sensitive strains ( $p = 0.008$ ). **Conclusions:** A high degree of carbapenem resistance in present study is alarming and poses therapeutic dilemmas for clinicians. Initiating timely and appropriate infection control measures along with a strictly implemented antibiotic stewardship program are necessary to prevent their spread.

**Keywords:** *Klebsiella pneumoniae*, carbapenem, KPC produces *Klebsiella pneumoniae*, Co morbid conditions

## INTRODUCTION

Antibiotics are life saving limited resources. They are used to treat serious infections to prevent morbidity and mortality. The indiscriminate and irrational use of antibiotics today has resulted in development of multidrug resistant strains in organisms commonly

associated with human infections.<sup>1,2</sup> Antibiotic resistance evolves naturally via natural selection through random mutation, but it could also be engineered by applying an evolutionary stress on a population. Once such a gene is generated, bacteria

can then transfer the genetic information in a horizontal fashion by plasmid exchange.<sup>3</sup> One of such gene is a KPC encoding gene. KPC is a class A carbapenemase enzyme which hydrolyzes broad spectrum beta lactum agents. The KPC encoding genes are plasmid mediated and thus have great potential for spread.<sup>4</sup> Resistance to carbapenem by such enzyme is a global concern due to limited therapeutic options and their association with life threatening infections. Large referral hospitals and teaching institutions are at great risk for a wide spread outbreak of infections and responsible for the spread of such strains from one location to another and to other hospitals. Thus, detection of these strains and knowledge about their prevalence is of utmost importance.

*Klebsiella pneumoniae* is ubiquitous in nature and can be isolated from soil, farm production and different water sources like lakes, rivers, sewage, fresh water. They are the component of the normal microflora in upper respiratory tract and gastrointestinal tract of human being and mice.<sup>5</sup> Keeping in mind the importance of *Klebsiella pneumoniae* as a human pathogen and their emerging carbapenem resistance, this study was undertaken to identify and characterize carbapenem resistant *Klebsiella pneumoniae* from various clinical samples. Efforts were also made to study the clinical details, particularly the associated risk factors, co-morbid conditions and outcome in patients infected with these strains.

## MATERIALS AND METHODS

This is a cross-sectional descriptive study, approved by institutional human research ethics committee of our institution. The study was conducted on a total number of 5455 clinical samples received and processed from indoor patients admitted in Shree Krishna Hospital, a tertiary care health centre located in rural part of Gujarat, India from May 2011 to April 2012. Informed consent was taken from patients when detailed clinical history was required. The study includes all the patients admitted in tertiary care hospital from whom *Klebsiella pneumoniae* were isolated from various clinical samples. Those specimens from where *Klebsiella pneumoniae* was isolated as laboratory contamination confirmed on the basis of clinical correlation were excluded. The isolates were identified to species level and

antimicrobial sensitivity was performed using miniAPI system according to Clinical and Laboratory Standards Institute (CLSI) 2011guidelines.<sup>6</sup> Ertapenem disc (10µg, Himedia, code-SD280-1VL) was used as surrogate marker for detection of carbapenem resistance. Ertapenem sensitivity was performed by disk diffusion method (CLSI 2011guidelines).<sup>6</sup> Isolates, that were found resistant to ertapenem, were considered as potential carbapenemase producers, confirmation of carbapenemase production was done with the Modified Hodge test.<sup>7-9</sup>

**The modified Hodge test (MHT):**<sup>7-9</sup> Mueller-Hinton agar plate was inoculated with a 1:10 dilution of a 0.5 McFarland suspension of *E.coli* ATCC 25922 and inoculated for confluent growth using a swab. A 10 µg Ertapenem disk was placed in the center, and each test isolate was streaked from the disk to the edge of the plate along with control strains.

After 16–24 hours at 37 C of aerobic incubation, plates were examined for a clover leaf-type indentation at the intersection of the test organism and the *E. coli* 25922, within the zone of inhibition of the carbapenem susceptibility disk. MHT positive test had a cloverleaf-like indentation of the *E.coli* 25922 growing along the test organism growth streak within the disk diffusion zone. MHT negative test had no growth of the *E.coli* 25922 along the test organism growth streak within the disc diffusion. Quality control was performed using control strains using MHT positive *Klebsiella pneumoniae* ATCC BAA-1705 and for negative control *Klebsiella pneumoniae* ATCC (American Type Culture Collection) 700603.

Patients were grouped into two categories; one included patients with infection by carbapenemase producing strains and other with infection by carbapenemase non -producing strains. Patient's clinical and demographic details were collected from the case files as well as by history taking and physical examination as and when required. *Klebsiella* infections are mostly seen in people with a weakened immune system. They may spread by inhalation or contact through skin or mucus membrane and are also spread by the indwelling devices or instruments used in procedures contaminated with *K. pneumoniae*. Many of these infections are obtained as nosocomial infections.

Data like age, sex, date of admission, date of culture isolate, presence of risk factors (age, sex, indwelling devices, duration of hospital stay, prior exposure to antibiotics) and co-morbid conditions (liver dysfunction, renal insufficiency, surgery/ invasive procedure in last 30 days, chronic lung disease, diabetes mellitus and heart disease), type of antibiotics given and response to therapy were collected. The co-morbid conditions were considered as per the clinical diagnosis with supporting laboratory data. Clinical outcome was evaluated in terms of length of hospital, stay after the diagnosis of infection, response to therapy and mortality. Death was considered due to infection when it occurred within two weeks from the diagnosis of infection with evidence suggestive of active infection and absence of any other fatal event. Patients were followed till discharged from the hospital. Infections caused by *Klebsiella pneumoniae* are treatable with antimicrobials like beta lactum, amino glycosides, quinolones, folic acid inhibitors, nitrofurantoin and carbapenems.

**Statistics:** The Master Chart of the data of the patients collected using the questionnaire was computerized on day to day basis on Micro Soft Excel 2007. Descriptive statistics was used to describe the observations of the study and Chi Square Test was applied as a test of significance. The Odds ratio was calculated wherever relevant. The tests of significance were calculated using SPSS Version 16 software.

## RESULTS

During the study period of a year, a total of 5455 clinical samples were processed from indoor patients with a culture positivity rate of 1571(28.8%). *Klebsiella pneumoniae* were isolated from 102 (6.5%) samples. *Klebsiella pneumoniae* were isolated more from male patients (68.6%) as compared to female patients (31.4%). Ertapenem resistant isolates in males (71%) were found to be more than in females (29%). Even KPC producing isolates in males (70.6%) were found more than females (29.4%). Respiratory sample was the major sample from which *Klebsiella pneumoniae* was isolated i.e. 41 (40.2%), followed by pus 24 (23.5%), urine 19 (18.6%) and blood 14 (13.7%). Distributions of Clinical samples in relation to ertapenem sensitivity are summarized in **Table 1**. Respiratory sample was the major sample from which *ertapenem resistant*

*Klebsiella pneumoniae* was isolated i.e. 11/102 (35.5%) followed by pus 10 (32.3%). Respiratory tract infection was the most common clinical condition in *Klebsiella pneumoniae* (37%) followed by soft tissue infections (21%) even in ertapenem resistant *Klebsiella pneumoniae* respiratory tract infection (35.5%) was common followed by soft tissue infections i.e. 25.8% .

**Table 1: Distribution of Clinical Sample in Relation to Ertapenem Sensitivity (n=102)**

Specimen	Ertapenem sensitive (%)	Ertapene Resistance (%)	Total (%)
Urine	13 (18.30)	6 (19.4)	19 (18.6)
Pus	14 (19.72)	10 (32.3)	24 (23.5)
Sputum/ET/	30 (42.25)	11 (35.5)	41 (40.2)
Blood	10 (14.08)	4 12.9)	14 (13.7)
Others	4(5.63)	0 (0.0)	4 (3.9)
<b>Total</b>	<b>71(69.6)</b>	<b>31 (30.4)</b>	<b>102 (100)</b>

**Table2: Distribution of Ertapenem Resistant *K. pneumoniae* in Different Locations (n=31)**

Specimen	MICU	NICU	SICU	Ward	Isolation & Burns Ward	Total
Blood	3	1	0	0	0	4
Pus	1	0	6	1	2	10
Sputum/ET/T	4	0	3	4	0	11
Urine	2	0	1	3	0	6
<b>Total</b>	<b>10</b>	<b>1</b>	<b>10</b>	<b>8</b>	<b>2</b>	<b>31</b>

The prevalence of ertapenem resistance is 30.4%. As seen in **Table 2**, the majority of ertapenem resistant i.e. 21 out of 31. (67.74%) *Klebsiella pneumoniae* were isolated from ICUs ((MICU, SICU, and NICU). Thus the location of patients in the hospital was found to be a significant risk for acquisition of infection by ertapenem resistant strains of *Klebsiella pneumoniae*. An association of Ertapenem resistant *Klebsiella pneumoniae* with different co-morbid conditions is shown in **Table 4**. Out of 102 *Klebsiella pneumoniae* isolated patients, 57 recovered, 29 worsened, nine died and seven patients were discharged against medical advice. Among nine patients who died, six were infected with ertapenem resistant strains. Sixty percent of those who were ertapenem resistant died or worsened while remaining 39.3% survived. Among those who

were ertapenem sensitive, 31% died or worsened. Adverse clinical outcomes (death or worsening) among ertapenem resistant patients was found to be statistically significant than ertapenem sensitive patients (p value 0.008).

Among 31 ertapenem resistant strains, 17 (16.6 %) were confirmed as KPC producers by Modified Hodge test. Twelve i.e. 70.6% of KPC producing *Klebsiella pneumoniae* were isolated from ICU

samples. Out of these six were isolated from pus swabs, six from respiratory secretions, four from urine and one from the blood. In 17 KPC strains, it was found that imipenem was sensitive in eight isolates, tetracycline sensitive in six isolates and co- trimoxazole sensitive in two isolates. Colistin and polymyxin were found to be sensitive in all 17 KPC isolates.

**Table 3: Association of Ertapenem Resistant *K. pneumoniae* with different co- morbid conditions (n= 31)**

Co-morbid condition	Ertapenem resistance		Ertapenem Sensitive		p value	Odds ratio (C.I)
	YES	NO	YES	NO		
Immunocompromised	12 (46.2%)	19 (25%)	14 (53.8%)	57 (75%)	0.04294	2.571 (1.015-6.514)
Surgery in last 30 days	9 (34.6%)	22(28.9%)	17 (65.4%)	54 (71.1%)	0.58750	1.299 (0.5036-3.353)
Previous hospitalization	14 (46.7%)	17 (23.6%)	16 (53.3%)	55 (76.4%)	0.02107	2.831(1.151-6.964)
Prior Antibiotic	14 (43.8%)	17 (24.3%)	18 (56.3%)	53 (75.7%)	0.04735	2.425 (0.9991-5.885)
Indwelling device	15 (42.9%)	16 (23.9%)	20 (57.1%)	51 (76.1%)	0.04790	2.391 (0.9978-.728)
ICU stay (days)	21 (38.9%)		33 (61.1%)		0.04783	2.418(0.9973-5.863)
Ward stay (days)	10 (20.8%)		38 (79.2%)			

## DISCUSSION

Globally ertapenem resistance in *Klebsiella* varies from 5-50% (**Table 3**). The prevalence of ertapenem resistance is 30.4% in our study. Resistance to imipenem and meropenem was high (33 & 100%, respectively) in ertapenem resistant isolates. So the prevalence of carbapenem resistance is on the high side in our study as compared to other studies conducted all over the world. The strategies recommended to prevent the spread of *Klebsiella spp* in document of CDC and Healthcare Infection Control practices Advisory Committee (HICPAC) is hand hygiene, contact precautions, patient and staff cohorting, healthcare personnel education, minimum use of invasive devices, promote antimicrobial stewardship and screening the patients<sup>15</sup>. Data regarding nosocomial infections reported to the CDC showed the prevalence of carbapenem resistance among *Klebsiella pneumoniae* Isolates increased from less than 1% in 2000 to 8% in 2007.<sup>16</sup> In New York City, it rose from 9% in 2002 to 18% in 2004, and then further to 38% in 2008.<sup>16</sup> Carbapenem resistance is increasing day by day. In India there is limited literature available regarding the prevalence of resistance to

carbapenems. Gupta *et.al* from Delhi reported 6.9% of Meropenem resistance and 4.3% of Imipenem resistance in *Klebsiella spp*.<sup>17</sup>

**Table 4: Prevalence of Ertapenem Resistant *Klebsiella* reported by different authors (2006-2012)**

Year of study	Place of study	Authors	Ertapenem Resistance*
2006	Boston	Hyle_EP <i>et al</i> <sup>10</sup>	32
2008	Taiwan	Jiunn-Jong Wu <i>et</i>	13.5
2008-09	Pondicherry	R.Mohamudha <i>et</i>	20.3
2008-09	Italy	Orsi_GB <i>et al</i> <sup>13</sup>	38
2010	Greece	A Zogorianou <i>et</i>	38.3
2012	India	present study	30.4

\*Ertapenem resistance in %

In one of the study conducted in India by R. Mohamudha Parveen *et al* 20.3% resistance to ertapenem has been reported.<sup>12</sup> The prevalence rates in our study are higher than other studies conducted in India. There is an increasing trend of prevalence of carbapenem resistance found in India in the recent past. In the Meropenem Yearly Susceptibility Test Information Collection Program (MYSTICP),

meropenem resistance among clinical isolates of *Klebsiella pneumoniae* increased significantly from 0.6% in 2004 to 5.6% in 2008. Among isolates reported to the National Healthcare, Safety Network (NHSN) in 2006–2007, carbapenem resistance was reported in up to 10.8% of *K. pneumoniae* isolates that were associated with certain device-related infections.<sup>18</sup>

In the present study, ertapenem resistant isolates in males 22 (71%) were found more than in females 9 (29%). Falagas *et al*, also reported similar sex distribution with carbapenem resistant *Klebsiella pneumoniae* infections.<sup>19</sup> In his study, males (71.6%) were more than females (28.4%). Even KPC producing isolates were found more in males (70.6%) than in females (29.4%). Maria Souli *et al*, also reported similar findings where out of 18 patient, 10 male patients (55.6%) were infected with KPC producing *Klebsiella pneumoniae*.<sup>20</sup>

There was a significant association of ertapenem resistant isolates in ICU patients, i.e. MICU (32.3%) and SICU (32.3%) as compared to patients in wards (p value = 0.048). such observations have not been shared by other investigators. We found an immunocompromised state (p= 0.043), prior antibiotics (p=0. 048), ICU stay (p=0. 048), more than one previous hospitalization (p=0. 01) and indwelling device use (p=0. 01) to have significant association with ertapenem resistance. There is a need to be very careful while selecting antibiotics in such cases and also need to have more scrutiny over such cases.

Mitchell J. Schwaber *et al*,<sup>21</sup> observed that when risk factors for the recovery of Carbapenem Resistance *Klebsiella pneumoniae* (CRKp) and Carbapenem Sensitive *Klebsiella pneumoniae* (CSKs) were compared; the prior receipt of antibiotics was the risk factor unique to the CRKp group. Orsi G B *et al*,<sup>13</sup> also found that prior use of certain antimicrobials, specifically carbapenems and cephalosporins, are primary independent risk factors for colonisation or infection with ertapenem resistance. Hyle EP *et al*,<sup>10</sup> observed that risk factors for ertapenem resistant enterobacteriaceae infection included intensive care unit (ICU) stay, exposure to any antibiotic during the 30 days prior to a positive culture result.

Adverse clinical outcomes (death or worsening in 60%) among ertapenem resistant patients was

found to be statistically significant than ertapenem sensitive patients (p value 0.008). In one of the case series describing the outcome of eight patients with CRKp infections in the surgical intensive care setting, six of eight patients died (75% mortality).<sup>19</sup> The study by Hyle EP *et al*,<sup>10</sup> showed that out of 62 case patients, 30-day outcomes from the time of positive culture result were 24 (39%) discharges, 10(16%) deaths, and 28 (44%) continued hospitalizations. The final end point of the hospitalization was discharged for 44 (71%) patients and death in 18 (29%) patients. Despite the universal concern regarding the emergence of outbreaks because of CRKp, there is a scarcity of information about risk factors and outcome for CRKp infections. It is a time to understand the risk factors and outcome of CRKp infections and prevent the spread by strict adherence to hospital infection control guidelines to prevent morbidity and mortality from such infections.

The prevalence of KPC producing *Klebsiella pneumoniae* is 16.6 % in hospitalized patients in our centre. It contributed to 54.8% of carbapenem resistance. As similar to our study, Varsha Gupta, *et al*<sup>22</sup> also reported 33.3% carbapenemase *Klebsiella pneumoniae* by modified Hodge's test and these isolates were 100% sensitive to colistin by disc diffusion. A study conducted in Greece (2010) by A Zogorianou *et al*,<sup>14</sup> reported 66.4% of KPC from 128 carbapenemase producing *Klebsiella pneumoniae* by molecular method. There is a high contribution of KPC in carbapenem resistance in our study. In our study, the number of KPCs from ICUs, i.e. 12 (70.5%) was more than non ICUs i.e. five (29.5%). In 17 KPC strains, it was found that colistin and polymyxin were found to be 100% sensitive followed by imipenem (47.06%), tetracycline (35.29%), cotrimoxazole (11.76%) and amikacin (11.76%). Varsha Gupta, *et al*<sup>22</sup> also reported 100% sensitivity to colistin and polymyxin. Maria Souli *et al*,<sup>20</sup> observed that more than 75% of KPC producers were sensitive to gentamicin, colistin and fosfomycin. Similar to our study, A Zogorianou *et al*<sup>14</sup> reported resistance to Amikacin 74%, ciprofloxacin 98%, co-trimoxazole 91% in KPC producing *Klebsiella pneumoniae*. P Gaibani *et al*<sup>23</sup> also observed that the KPC-positive strains were resistant to beta-lactams (including the 3rd

and 4th generation cephalosporins) and to fluoroquinolones, some of them are sensitive to tetracycline and co-trimoxazole. Some of the KPC-producing strains were still susceptible to antimicrobials (cotrimoxazole, tetracycline) that are not commonly used as alternative therapy for the treatment of nosocomial infections caused by to MDR (Multi Drug Resistant) gram-negative organisms. So culture and antibiotic sensitivity are utmost important to know the drug resistance in any infection caused by *Klebsiella pneumoniae*.

## CONCLUSION

We found a high prevalence of KPC producing *Klebsiella pneumoniae* with high degree of antimicrobial resistance in our study. This is a challenge for clinicians as well as for administrators. Formulating an antimicrobial policy and its strict implementation with regular surveillance of KPC producing isolates is needed along with appropriate infection control measures to curtail its emergence and spread.

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