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Original Research Article

Antimicrobial susceptibility pattern and phenotypic detection of metallo-beta lactamases in *K. pneumoniae* isolates in a tertiary care hospital

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ABSTRACT

Background: *K. pneumoniae* is the most important pathogen causing community as well as nosocomial infections. The study was conducted with the aim to study antimicrobial susceptibility pattern of *K. pneumoniae* isolates as well as to detect MBL in carbapenem resistant isolates.
Methods: The study was conducted for a period of six months from October 2021 to March 2022. All isolates of *K. pneumoniae* were obtained from various clinical samples. Antimicrobial susceptibility testing was done by Vitek 2 Compact system. Metallo β-lactamase detection was done by imipenem-EDTA combined disk method.
Results: Out of total 1336 growth positive isolates, 248 isolates were of *K. pneumoniae*. From total 248 isolates, 162 were obtained from male patients and 86 were obtained from female patients. Maximum number (97) of isolates was obtained from age group of 61-80 years. Maximum (30.24%) isolates of *K. pneumoniae* were from urine and minimum (4.43%) from body fluids. Isolates were highly resistant towards antimicrobials tested whereas moderate sensitivity was reported for ertapenem, imipenem, meropenem and gentamicin. Isolates were highly sensitive to colistin followed by amikacin and tigecycline. MBL production was observed in 84.5% carbapenem resistant isolates.
Conclusions: This present study highlighted that multidrug resistant strains of *K. pneumoniae* are common in tertiary care hospitals. Unwarranted and unrestricted usage of antimicrobials is associated with growing emergence of resistance. Therefore, regular monitoring of carbapenem resistance is important for developing strategies to control infections caused by *K. pneumoniae*.

Keywords: Carbapenems, Combined disc method, Imipenem-EDTA, *K. pneumoniae*, Metallo betalactamase

INTRODUCTION

K. pneumoniae is the most important pathogen which causes community as well as hospital acquired infections. The various infections caused by *K. pneumoniae* are pneumonia, urinary tract infections (UTIs), surgical site infections (SSIs), blood stream infections (BSIs), hepatobillary infections and much more.[1] *K. pneumoniae* had gained great attention of scientific world due to severity of disease caused and resistance to various antimicrobials so difficulty in treatment. There is an increasing number of multi drug resistant (MDR) and extremely drug resistant (XRD) *K. pneumoniae* being reported, possessing a great concern to field of medicine.[2,3] Cephalosporins, clotrimazole, tetracycline and fluoroquinolone were the drugs used against ESBL producing bacteria, but production of metallo-beta-lactamases (MBLs) by *K. pneumoniae* strains led it to be resistant against carbapenems also. Resistance is mediated by carbapenemase such as MBLs, including IMP, VIM and NDM as well as by plasmid-mediated clavulanic acid-inhibited class A beta-lactamase like *K. pneumoniae* carbapenemase (KPC) and GES. Horizontal gene transfer (HGT) is conferring high level resistance to antibiotics of the type β-lactams and quinolones.[4] Amber class B are zinc dependent metallo-beta lactamases and have the ability to hydrolyse all beta-lactams including penicillin's, cephalosporin's and carbapenems with aztreonam being exception and they are inhibited by metal chelators like EDTA and dipicolinic acid.[5,6]

Early detection of MBL producing isolates of *K. pneumoniae* is important in order to set up appropriate antimicrobial therapy as well as to prevent their inter and intra healthcare setting transmission.[7] There are various molecular, biochemical and phenotypic techniques available in the current era which can detect metallo-beta lactamases. Genetic methods for detection of production of metallo beta-lactamases by polymerase chain reaction (PCR) usually give highly accurate and reliable results but due to cost and labor constrain this method is of limited practical use for daily use.[8,9] As it has been reported that MBL activity is dependent on zinc or cadmium there are various phenotypic methods available. Phenotypically MBL activity is investigated using following methods; imipenem-EDTA combination disc test (CDT), different double disk synergy, test for imipenem and meropenem along with EDTA or 2-marcaptopropionic acid (2MPA) disc (DDST), modified Hodge test (MHT) and E-test. Phenotypic methods are easy to perform and economic with good results. These tests are also recommended by CLSI as general phenotypic methods for detection of carbapenemases.[10-12]

The combined imipenem-EDTA (ethylenediamine tetraacetic acid) (CDT) works by comparing the zone of inhibition obtained with imipenem (IPM) disc with and without IMP-EDT disc. The method (CDT) is reported as reliable for detection of MBL in carbapenem resistant strains.[13]

The present study was carried with an objective to isolate *K. pneumoniae* from various clinical samples, perform antimicrobial susceptibility testing and detect production of metallo betalactamase enzyme in carbapenem resistant *K. pneumoniae* isolates.

METHODS

It was a cross-sectional study conducted at the Department of Microbiology, Adesh Institute of Medical Sciences and Research (AIMSR) Bathinda, Punjab for a period of six months from 1st October 2021 to 31st March 2022.

Sampling technique

The samples were collected using random sampling technique.

Selection criteria

K. pneumoniae isolates obtained on bacterial culture from various clinical samples received from male and female patients admitted in various ICU's, wards and OPD including all age-groups.

Exclusion criteria

All other isolates obtained on bacterial culture from various clinical samples received from male and female patients admitted in various ICU's, wards and OPD including all age-groups.

Procedure

Various clinical samples like urine, pus, sputum and other respiratory samples (endotracheal secretions, ET tubes/ET secretions, tracheal aspirates, BAL), blood and other body fluids (CSF, pleural fluid, ascitic fluid, pericardial fluid, peritoneal fluid, synovial fluid) were received in sterile container in bacteriology section of microbiology laboratory. All the samples were processed as per standard microbiological procedures.[14,15]

The blood and other sterile body fluid samples were inoculated into the Bact/Alert standard aerobic bottles. The inoculated bottles were loaded into the Bact/Alert and were incubated for a maximum period of 5 days.[14] Positive samples were further sub-cultured on blood agar and MacConkey agar media and incubated at 37°C. Growth was examined after overnight incubation. The urine, pus and respiratory samples were directly inoculated on Blood agar and MacConkey agar media.[15] *K. pneumoniae* species were identified on the basis of colony characteristics, Gram staining morphology and motility. Further confirmation was done by biochemical tests such as Catalase, IMVIC tests (indole, MR, VP, and citrate), Urease, TSI, and Oxidase.[15] Antimicrobial susceptibility testing was performed using N280 card by VITEK 2 compact system as recommended by Clinical and Laboratory Standards Institute (CLSI) guidelines.[16]

MBL detection was done phenotypically by IMP-EDTA combined disk test as described by Yong et al.[12] Test organisms were inoculated on to plates with Mueller Hinton agar as recommended by the CLSI. Two discs (HIMEDIA)- imipenem and imipenem-EDTA (10 µg and 750 µg) were placed on the plate 20 mm apart. The inhibition zones of the imipenem and imipenem-EDTA disks were compared after 16 to 18 hours of aerobic incubation at 37°C. The zone difference between the Imipenem and Imipenem/ EDTA discs of diameter >7 mm was interpreted as positive for MBL production.[5]

248 samples of *K. pneumoniae* were isolated.

Ethical approval

The study was approved by Ethics Committee for Biomedical and Research of Adesh University.

Statistical analysis

The data analysis was done by descriptive statistics by calculating ratios and percentages, pie charts and bar graphs using Microsoft word and excel.

RESULTS

A total of 4724 clinical samples from various departments were received out of which 1336 showed growth. Out of 1336 growth positive isolates, 248 isolates were of *K. pneumoniae*. The isolation rate of *K. pneumoniae* from total processed samples came out to be 5.24% (248/4724) and from 1336 growth positive samples the isolation rate of *K. pneumoniae* came out to be 18.56% (248/1336). More number of isolates of *K. pneumoniae* (65.32%) was obtained from male patients as compared to female patients (34.67%). Maximum number 97 (39.11%) of *K. pneumoniae* were obtained from age group of 61-80 years followed by age group of 41-60 years; 21-40 years; 0-20 years and minimum isolates were obtained from age group >80 years (Table 1).

Table 1: Age group wise distribution of *K. pneumoniae* isolates.

Age group in years	*K. pneumoniae* isolates (n=248)
0-20	19 (7.6%)
21-40	44 (17.7%)
41-60	82(33.3%)
61-80	97 (39.0%)
>80	6 (2.4%)

Table 2: Department wise distribution of *K. pneumoniae* isolates.

Department	Number of isolates (n=248)
ICU's	165 (66.5%)
Surgery	28 (11.3%)
Medicine	22 (8.8%)
Emergency	18 (7.2%)
OBG	7 (2.8%)
Urology	3 (1.2%)
ENT	3 (1.2%)
Pediatrics	2 (1.0%)

Table 3: Respective isolation rates of *K. pneumoniae* from various samples.

Specimen	*K. pneumoniae* (n=248)
Urine	75 (30.24%)
ET tube/ET secretions	69 (27.82%)
Other respiratory samples (sputum, BAL)	33 (13.30%)
Blood	32 (12.90%)
Pus/wound swab	28 (11.29%)
Body fluids	11 (4.43%)

66.5% isolates were obtained from ICU patients followed by other departments (Table 2).

Maximum isolates of *K. pneumoniae* were obtained from urine samples (30.24%) and minimum from body fluids (4.43%) (Table 3).

Antibiogram of K. pneumoniae

K. pneumoniae isolates were found to be highly resistant towards amoxicillin/clavulanic acid (90.7%), piperacillin/ tazobactum (90.2%), cefuroxime (96.8%), cefuroxime axetil (96.8%), ceftriaxone (95.5%), cefoperazone/ sulbactum (87.0%), cefepime (92.7%), ciprofloxacin (89.6%), cotrimoxazole (85.1%) However isolates of *K. pneumoniae* were highly sensitive to colistin (95.6%), followed by amikacin (76.7%) and tigecycline (63.7%). (Table 4).

Table 4: Antibiogram of *K. pneumoniae* (n=248).

Antibiotic tested	No. of sensitive isolates (% sensitivity)	No. of resistant isolates (% resistance)
Amikacin	190 (76.7)	58 (23.2)
Gentamicin	79 (31.9)	169 (68.1)
Ciprofloxacin	26 (10.4)	222 (89.6)
Cefuroxime axetil	8 (3.2)	240 (96.8)
Ceftriaxone	11 (4.5)	237 (95.5)
Cefepime	18 (7.3)	230 (92.7)
Cefoperazone/ sulbactam	30 (13.0)	218 (87. 0)
Amoxicillin/ clavulanic acid	23 (9.3)	225 (90.7)
Piperacillin/ tazobactam	24 (10.8)	224 (90.2)
Imipenem	54 (21.7)	194 (78.3)
Ertapenem	53 (21.3)	195 (78.7)
Meropenem	53 (21.3)	195 (78.7)
Cotrimoxazole	37 (14.9)	211 (85.1)
Tigecycline	158 (63.7)	90 (36.3)
Colistin	237 (95.6)	11 (4.4)

MBL production in K. pneumoniae

Out of total 194 carbapenem resistant isolates of *K. pneumoniae*, MBL production was observed in 164 (84.5%) isolates (Figure 1).

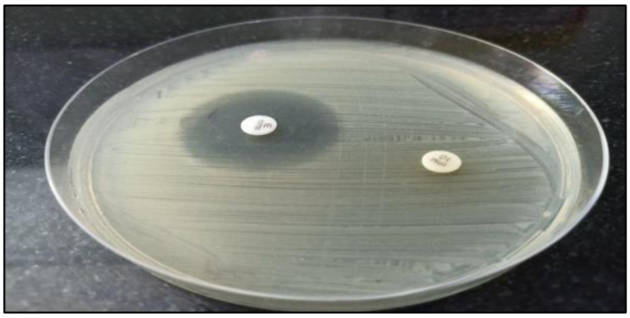

Figure 1: Mueller Hinton plate with imipenem and imipenem-EDTA disc showing MBL positive *K. pneumoniae*.

DISCUSSION

In the present study a total of 4724 clinical samples from various departments were received and out of these 1336 showed growth. Out of 1336 growth positive isolates, 248 isolates were of *K. pneumoniae. The* isolation rate of *K. pneumoniae* from total processed samples came out to be 5.24% (248/4724) and from 1336 growth positive samples the isolation rate of *K. pneumoniae* came out to be 18.56% (248/1336). The prevalence correlates to great extent with the studies by Nirwati et al, Gill et al, Farkhanda et al, Sodhi et al, Sonia et al and Odari et al who reported prevalence to be 17.36%, 22.43%, 15.18%, 21.23%, 23.73% and 15.7% respectively.[17-22] However, Pyakurel et al reported prevalence 31.4% which is higher than the present study.[23] Maximum isolates of *K. pneumoniae* were obtained from urine (30.24%), followed by ET tubes/ET secretions (27.82%), other respiratory samples (13.30%), blood (12.90%) pus and wound swabs (11.29%) and minimum from body fluids (4.43%). The study almost correlates with the studies by Naqid et al who reported maximum isolation of the *K. pneumoniae* from urine samples 66.2%, followed by the blood samples 12.3%, and wound swabs 10%, respiratory samples (9.2%), other samples (2.3%).[24] Indrajith et al also reported maximum isolates (29%) were from urine, followed by Sputum (25.85%), blood (25%), pus (17%) and biopsy specimen (3%).[25] Ssekatawa et al also reported highest number (56.4%) of *K. pneumoniae* isolates from urine, followed by pus swabs (21.1%), from blood (10.12%), rectal swabs (7.0%), vaginal swabs (3.08%), and 1.0% each from tracheal aspirate and sputum.[26] However the study by Sathyavathy and Madhusudhan reported 50% isolates from wound/pus followed by urine (27%), sputum (14%), and blood (9%) which shows discordance with the present study.[27]

In the present study, out total 248 isolates of *K. pneumoniae*, 65.32% isolates were obtained from male patients and 34.67% were obtained from female patients. The study is quite similar to the studies done by Bhavsar et al, who reported 64.5% isolated from male patients and 35.5% from female patients.[28] Su et al, also reported 63.2% isolates from male and 36.8% female patients.[29] However Muzaheed et al, reported higher number of isolates from male patients (80.1%) and lesser from female patients (19.8%).[30] In the present study maximum isolates of *K. pneumoniae* were obtained from ICU patients (66.5%). Gupta et al, Pyakurel et al and Su et al have reported isolation rate of *K. pneumoniae* 70%, 55.1% and 20.6% from ICU samples respectively.[23,29,31]

In the present study the pattern of resistance shown by *K. pneumoniae* towards various antimicrobials was reported as following amoxicillin/clavulanic acid (90.7%), imipenem (78.3%), meropenem (78.7%), ceftiaxone (95.5%), ciprofloxacin (89.6%), amoxicillin/clavulanic acid (90.7%), cotrimoxazole (85.1%), however isolates were highly sensitive to colistin (95.6%) followed by amikacin (76.7%) and tigecycline (63.7%). Tian et al in a study reported 95.8% resistance by *K. pneumoniae* isolates towards imipenem, 95.2% towards meropenem, 62% for ciproflaxin Effah et al reported the resistance pattern towards ciprofloxacin (59.8%), imipenem (65.6%), and meropenem (63%).[32,33] Oladipo et al reported 97% resistance towards ciprofloxacin; Khalifa et al reported resistance of 88.6% towards ceftriaxone, amoxicillin/clavulanic and cotrimoxazole, resistance towards imipenem was reported as 66%.[34,35] Sensitivity of *K. pneumoniae* isolates towards amikacin was reported as 42%, 90.24%, 95.2%, and 86% by Tian et al, Farkhanda et al, Nirwati et al and Kashefieh et al respectively.[17,22,32,36] Sensitivity of *K. pneumoniae* towards colistin has been reported to be higher by various other studies- 89.42% and 88.5% which almost co relates with the present study.[37,38]

Out of total 194 carbapenem resistant isolates of *K. pneumoniae,* MBL production was observed in 164 (84.5%) isolates. The results of present study are almost correlating with the studies done by Bora et al, Agrawal et al, Javed et al, Gupta et al who had reported MBL positivity as 71%, 62.5%, 67.1% and 71.5% MBL production in *K. pneumoniae*.[31,39-41] Hoang et al had reported 95% MBL production in *K. pneumoniae* isolates, which is quite higher as compared to this study.[42]

The study was conducted for a period of six months only and single phenotypic method was used for detection of MBL's. Therefore, the lesser sample size as well as lack of investigation by other MBL detection methods can be mentioned as limitations of the present study.

CONCLUSION

The isolation rate of *K. pneumoniae* as indicated by present study as well as various studies indicates their major role in nosocomial infections and also as an etiological agent in community acquired infection. In the present study high rate of resistance was observed to broad-spectrum cephalosporin, aminoglycosides, fluoroquinolones and even combinations of penicillin/beta-lactamase inhibitor. The present study also revealed high proportion of MBL producing *K. pneumoniae* isolates in this hospital.

Therefore, early detection and infection control practices are the best defenses against these organisms and systematic surveillance to detect MBL producers is necessary. It is most important to follow antibiotic restriction policies to avoid excessive use of carbapenems in order to prevent going towards the era with no antibiotics.

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