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Original Researcher Article

Phenotypic and Genotypic Characterization of Carbapenemase-Producing Escherichia coli and Klebsiella pneumoniae and Their Antibiotic Sensitivity Profiles

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Abstracts: ***Background*:** Carbapenem-resistant Enterobacterales, particularly *Escherichia coli* and *Klebsiella pneumoniae*, pose a serious global health threat due to limited treatment options and high morbidity and mortality. ***Aim*:** To perform phenotypic and genotypic characterization of carbapenemase-producing *E. coli* and *K. pneumoniae* and assess their antimicrobial susceptibility profiles. ***Methodology*:** A descriptive laboratory-based study was conducted over 18 months in a tertiary care hospital. A total of 200 non-repeat clinical isolates (100 *E. coli* and 100 *K. pneumoniae*) resistant to at least one carbapenem were included. Antimicrobial susceptibility testing was performed by Kirby–Bauer method. Carbapenemase production was detected phenotypically using Modified Hodge Test, MBL, and KPC tests, while genotypic detection of blaNDM and blaKPC genes was done by PCR. ***Results*:** High resistance was observed to carbapenems, cephalosporins, and fluoroquinolones in both organisms. Carbapenemase production was common, with MBLs predominating. The blaNDM gene was the most frequently detected resistance determinant. ***Conclusion*:** The study reveals a high burden of carbapenem-resistant *E. coli* and *K. pneumoniae*, predominantly driven by blaNDM, underscoring the need for routine molecular surveillance and strengthened antimicrobial stewardship.

Keywords*: Antimicrobial resistance, Carbapenem resistance, Escherichia coli, Klebsiella pneumoniae, blaNDM.*

INTRODUCTION

Antimicrobial resistance (AMR) has become a serious global public health issue and has been recognized as one of the greatest challenges of the 21 century, as it is leading to a failure of prevention and treatment of several categories of bacterial infections efficiently [1]. The carbapenem-resistant Enterobacterales (CRE), among the resistant pathogens, are of particular concern as they are linked to a high rate of morbidity, mortality, prolonged hospital stays, and

increased healthcare costs, thus forming a very alarming group of' pathogens. In general, carbapenem drugs are considered to be 'the last option for treating severe infections caused by multidrug-resistant Gram-negative bacteria; hence, the emergence of carbapenem resistance and its rapid spread will greatly reduce the number of remaining therapeutic options [2]. *Escherichia coli* and *Klebsiella pneumoniae,* the two most important clinically relevant members of the Enterobacterales family, are also the most commonly isolated bacteria from carbapenem-related infections throughout the world.

E. coli and *K. pneumoniae* are often responsible for infections acquired in the community as well as through health care, among which are urinary tract infections, blood infections, pneumonia, intra-abdominal infections, and sepsis [3]. Although *E. coli* breeds in nature within the human gut as a commensal organism, pathogenic strains can be extremely lethal especially to the already weak immune system individuals. In contrast to E. coli, *K. pneumoniae* is a notorious opportunistic pathogen whose outbreaks are concentrated in hospitals, particularly in ICUs. The emergence of carbapenem resistance in these bacteria has become a serious concern that is mainly due to antibiotic pressure and also to the horizontal transfer of resistance genes among bacteria, as it poses a challenge to infection control and antimicrobial stewardship [4].

The resistance of *E. coli* and *K. pneumoniae* to carbapenems has several sources, among them decreased membrane permeability, enhanced pumping out of drugs, and the most important one, the production of carbapenemase enzymes [5]. Carbapenemases are β-lactamases, which can hydrolyze carbapenems and other β-lactam antibiotics, and as a result, these antibiotics are rendered non-effective. The enzymes are divided into various molecular classes according to the Ambler classification, with class A (e.g., KPC), class B metallo-β-lactamases (e.g., NDM, VIM, IMP), and class D oxacillinases (e.g., OXA-48-like enzymes) being the most clinically important. The genes for these enzymes are frequently found on plasmids and other mobile genetic elements, which promote their quick transfer not only among bacteria but also across different regions of the globe [6].

The identification and characterization of *E. coli* and *K. pneumoniae* that produce carbapenemase are very important for patient management, infection control, and epidemiological surveillance. Dependable phenotypic methods still form the basis of' the routine laboratory diagnosis and comprise antimicrobial susceptibility testing, screening for 'reduced carbapenem susceptibility, and confirmatory assays like the modified carbapenem inactivation method (mCIM), Carba NP test, and inhibitor-based tests. These methods not only provide information about the functional expression of the enzyme responsible for carbapenem resistance but also influence the initial choice of therapy [7]. Despite this, phenotypic testing may occasionally show low specificity or may not provide the exact type of carbapenemase, especially for isolates with weak expression or multiple resistance mechanisms.

Genotypic characterization supports phenotypic approaches by letting the exact carbapenemase-encoding genes be identified via molecular means like polymerase chain reaction (PCR) and sequencing [8]. Genotypic method not only affirms the presence of certain resistance genes but also helps in knowing the molecular epidemiology and the transmission dynamics of carbapenem-resistant strains. It is very important to know which carbapenemase genes are present among the clinical isolates in order to trace the resistance patterns that have emerged, detect outbreaks, and apply infection prevention measures that are specifically targeted, thus enabling the effective management of the situation.

The evaluation of the antibiotic sensitivity profiles of carbapenemase-producing isolates, besides the identification of resistance mechanisms, is crucial for the modern medical practice [9]. Such bacteria often have a multi-drug resistance problem that involves different classes of antibiotics such as cephalosporins, fluoroquinolones, and aminoglycosides, which imposes limited options for treatment, but still, the number of patients susceptible to certain drugs like colistin, tigecycline, fosfomycin, and newer β-lactam/β-lactamase inhibitor combinations will depend on the resistance genotype and local antimicrobial usage patterns. Therefore, complete antibiotic sensitivity profiling is very important in the process of supporting the right therapy and bringing about the best clinical outcomes [10].

The current investigation is intended to be exhaustive in the phenotypic and genotypic characterization of carbapenemase-producing *Escherichia coli* and *Klebsiella pneumoniae* from clinical samples, besides a study of their antibiotic resistance patterns. This research intends to merge the phenotypic detection techniques with the molecular typing of carbapenemase genes thereby to offer a deeper understanding of the given resistance mechanisms and

to suggest data that could be useful in the context of' antimicrobial stewardship programs as well as infection control strategies. The above-mentioned understanding is crucial in 'the fight against the ever-increasing threat of carbapenem-resistant pathogens and thus helping to keep the existing antibacterial agents effective.

METHODOLOGY

2.1 Study Design

This study was a descriptive, laboratory-based observational study aimed at phenotypic and genotypic characterization of carbapenemase-producing *Escherichia coli* and *Klebsiella pneumoniae*, along with evaluation of their antibiotic sensitivity profiles.

2.2 Study Area

The study was carried out in the Department of Microbiology of a tertiary care hospital, in collaboration with a molecular diagnostic laboratory. The hospital caters to patients from both urban and rural backgrounds and includes outpatient departments, inpatient wards, and intensive care units (ICUs).

2.3 Study Period

The study was conducted over a period of one and a half years.

2.4 Study Participants

The study participants consisted of clinical isolates of *Escherichia coli* and *Klebsiella pneumoniae* obtained from patients attending various clinical departments of' the hospital.

Inclusion Criteria

- Non-'repeat, consecutive clinical isolates of *Escherichia coli* and *Klebsiella pneumoniae*
- Isolates recovered from clinical specimens such as urine, pus, blood, tracheal aspirates, and ascitic fluid
- Samples obtained from patients of all age groups and both sexes
- Isolates showing resistance to at least one carbapenem antibiotic (imipenem, meropenem, or ertapenem)

Exclusion Criteria

- Duplicate isolates from the same patient
- Environmental or surveillance isolates
- Isolates other than *Escherichia coli* and *Klebsiella pneumoniae*
- Poorly preserved or contaminated samples

2.5 Sample Size

A total of 200 non-repeat clinical isolates were included in the study, comprising 100 isolates of *Escherichia coli* and 100 isolates of' *Klebsiella pneumoniae*.

2.6 Procedure

The clinical samples that arrived at the microbiology laboratory were processed using the standard microbiological techniques. The isolation and identification of *Escherichia coli* and *Klebsiella pneumoniae* were done through a series of methods that included examination of colony characteristics on media, Gram staining, and standard biochemical tests.

The antimicrobial susceptibility testing was performed on Mueller-Hinton agar by the Kirby-Bauer disc diffusion method, and the result interpretation was in accordance with the CLSI (Clinical and Laboratory Standards Institute) 2014 guidelines. Among the tested antibiotics were the most widely used antimicrobial agents, giving priority to the carbapenems imipenem, meropenem, and ertapenem. Bacterial isolates that were resistant to any of the carbapenems were considered to be carbapenem-resistant.

The Modified Hodge Test (MHT) was applied for the phenotypic detection of carbapenemase production as per CLSI recommendation. The detection of metallo-β-lactamase (MBL) production was accomplished using the disk potentiation test that made use of the imipenem and imipenem-EDTA disks. A combined disk test was conducted for the confirmation of *K. pneumoniae* carbapenemase (KPC) production, in which imipenem alone and imipenem supplemented with phenylboronic acid were used.

Genotypic characterization was done employing conventional Polymerase Chain Reaction (PCR) techniques. The specific primers were used for the detection of the presence of the genes blaNDM and blaKPC that encode for the carbapenemase. The primers for other carbapenemase genes like blaIMP, blaVIM, and blaOXA could not be used in the study because of' the limited budget.

2.7 Statistical Analysis

Data obtained from phenotypic and genotypic 'tests, along with antimicrobial susceptibility patterns, were compiled and entered into Microsoft Excel. Descriptive statistical analysis was performed, and results were expressed in terms of frequencies and

percentages. Appropriate tables and figures were used to present the findings clearly.

RESULT

The breakdown of clinical *E. coli* and *K. pneumoniae* isolates is presented in Table 1. Out of 200 isolates, urine was by far the most common source accounting for as much as (37.5%) 75 isolates with even *E. coli* (45%) being more than *K. pneumoniae* (30%), and thus its dominance in urinary tract infections is confirmed. Pus samples made up 45 (22.5%) of the total isolates, where *K. pneumoniae* (25%) was slightly ahead of *E. coli* (20%). Blood samples contained 35 isolates (17.5%), again revealing a predominance of *K. pneumoniae* over E. coli. Tracheal aspirates had 25 isolates (12.5%), with *K. pneumoniae* being the main isolate suggesting its link to respiratory infections. Different from the other sources, ascitic fluid samples accounted for the least frequency (10%) with equal distribution of the two organisms. Thus, the table clearly shows the urine sample type as the main one and also reveals the different patterns in the isolation of the two pathogens from various clinical specimens.

Table 1: Distribution of Clinical Isolates Based on Sample Type

Sample Type	*E. coli* (n=100)	*K. pneumoniae* (n=100)	Total (n=200)
Urine	45	30	75
Pus	20	25	45
Blood	15	20	35
Tracheal aspirate	10	15	25
Ascitic fluid	10	10	20
Total	**100**	**100**	**200**

In Table 2, the sensitivity of' 100 *Escherichia coli* isolates to different antimicrobial agents is shown and it is seen 'that there is a considerable diversity in the antibiotics used for testing. Amikacin was the most susceptible with 62%, then came gentamicin with 55%, which suggested that aminoglycosides were relatively more effective against the tested bacteria. On the other hand, the fluoroquinolone and cephalosporin antibiotics were very poorly tolerated, with only 28% of the bacteria being susceptible to ciprofloxacin, while the third-generation cephalosporins, cefotaxime (20%) and ceftazidime (18%), had very significant resistance rates. The piperacillin–tazobactam combination, a beta-lactam/beta-lactamase inhibitor, was somewhat effective, with a 40% sensitivity. What is even worse is that the resistance to carbapenems was also quite high, as the sensitivities of imipenem, meropenem, and ertapenem were only 30%, 32%, and 25%, respectively. The table gives a summary of the situation that a great deal of bacterial resistance to drugs has been developed in *E. coli*, which not only limits the treatment of infection but also raises the issue of the necessity of good antibiotic use and continuous monitoring of the resistance

Table 2: Antimicrobial Susceptibility Pattern of *Escherichia coli* Isolates (n=100)

Antibiotic	Sensitive n (%)	Resistant n (%)
Amikacin	62 (62%)	38 (38%)
Gentamicin	55 (55%)	45 (45%)
Ciprofloxacin	28 (28%)	72 (72%)
Cefotaxime	20 (20%)	80 (80%)
Ceftazidime	18 (18%)	82 (82%)
Piperacillin–Tazobactam	40 (40%)	60 (60%)
Imipenem	30 (30%)	70 (70%)
Meropenem	32 (32%)	68 (68%)
Ertapenem	25 (25%)	75 (75%)

As depicted in Table 3, the antimicrobial susceptibility pattern among the *Klebsiella pneumoniae* isolates (n=100) is as of high concern and was characterized by high levels of' resistance to almost all antibiotics that were tested. However, aminoglycosides did show moderate activity, with amikacin being equally sensitive and 'resistant (50% each) among the isolates and gentamicin having the least sensitivity (42%). The fluoroquinolone resistance was very high since only 22% of the isolates were sensitive to ciprofloxacin. The third-generation cephalosporins were almost totally ineffective with the sensitivity rates standing at only 15% for cefotaxime and 12% for ceftazidime indicating the existence of a major resistance problem. Piperacillin-tazobactam was still somewhat effective but only in a limited number of isolates (35%). Also of interest is that carbapenems were less sensitive too with the sensitivity rates being 25% for imipenem, 28% for meropenem, and 20% for ertapenem thus drawing attention to the fact that there is a large number of carbapenem-resistant K pneumoniae in circulation and also indicating that prudent antibiotic use and bolstered antimicrobial stewardship are definitely required.

Table 3: Antimicrobial Susceptibility Pattern of *Klebsiella pneumoniae* Isolates (n=100)

Antibiotic	Sensitive n (%)	Resistant n (%)
Amikacin	50 (50%)	50 (50%)
Gentamicin	42 (42%)	58 (58%)
Ciprofloxacin	22 (22%)	78 (78%)
Cefotaxime	15 (15%)	85 (85%)
Ceftazidime	12 (12%)	88 (88%)
Piperacillin–Tazobactam	35 (35%)	65 (65%)
Imipenem	25 (25%)	75 (75%)
Meropenem	28 (28%)	72 (72%)
Ertapenem	20 (20%)	80 (80%)

Table 4 presents the phenotypic detection of carbapenemase production in *E. coli* and *K. pneumoniae* isolates, which were both made up of 100 samples. The Modified Hodge Test revealed that a considerable number of isolates were subjected to carbapenemase production, with 65% of *E. coli* and 72% of *K. pneumoniae* giving positive results. The imipenem-EDTA test, which detects MBL production, identified 40% of' *E. coli* and 45% of *K. pneumoniae* isolates as non-susceptible to imipenem due to MBL, thus *K. pneumoniae* getting more abundance of MBLs. KPC production as detected by 'the boronic acid test was comparatively less but still significant as it was seen in 18% of *E. coli* and 22% of K. pneumoniae. Carbapenemase activity was not found in 17% of *E. coli* and 11% of *K. pneumoniae* isolates; this may point out that during *E. coli* non-carbapenemase mechanisms of resistance might be also contributing, especially among them.

Table 4: Phenotypic Detection of Carbapenemase Production

Phenotypic Test	*E. coli* (n=100)	*K. pneumoniae* (n=100)
Modified Hodge Test (Positive)	65	72
MBL detected (Imipenem + EDTA)	40	45
KPC detected (Boronic acid test)	18	22
Carbapenemase not detected	17	11

Table 5 illustrates the results of PCR genotypic detection of carbapenemase genes in *E. coli* and *K. pneumoniae* isolates. The blaNDM gene was the most prevalent carbapenemase gene detected in both species, being responsible for 38% of *E. coli* and 42% of *K. pneumoniae*. The blaKPC gene was detected in a lower percentage of the isolates, with 15% for *E. coli* and 20% for K. pneumoniae. The co-occurrence of the blaNDM and blaKPC genes was found in 7% of *E. coli* and 10% of' *K. pneumoniae*, implying the presence of

various ‘resistance mechanisms in a limited number of isolates. Most importantly, no carbapenemase gene was identified in 40% of *E. coli* and 28% of K. pneumoniae, which means the possibility of other resistance mechanisms being involved.

Table 5: Genotypic Detection of Carbapenemase Genes by PCR

Carbapenemase Gene	*E. coli* n (%)	*K. pneumoniae* n (%)
blaNDM	38 (38%)	42 (42%)
blaKPC	15 (15%)	20 (20%)
Both genes present	7 (7%)	10 (10%)
No gene detected	40 (40%)	28 (28%)
Total	**100 (100%)**	**100 (100%)**

DISCUSSION

The study at hand brings to attention the significant and increasing issue of the existence of multidrug-resistant (MDR) *Escherichia coli* and Klebsiella pneumoniae, particularly the carbapenem-resistant strains, in a tertiary care center. Just like reports from the entire world and India, the emergence of carbapenem resistance among Enterobacterales is a major obstacle in terms of therapy and control of infections due to the scarcity of available treatments and the high rates of morbidity and mortality associated with this issue (Ventola, 2015; Meletis, 2016). The dominance of urinary isolates in this research, predominantly E. coli, is consistent with its recognized position as the foremost culprit of’ urinary tract infections, whereas the increased ‘recovery of *K. pneumoniae* from the blood, pus, and respiratory samples highlights its role as a hospital-acquired and invasive pathogen (Sikora & Zahra, 2023) [11].

In the current study, the ratios of resistance to sensitivity to carbapenems were 1.5:1 for *E. coli* and 1.6:1 for K. pneumoniae. More precisely, the disk diffusion tests indicated that 40% of *E. coli* and 38.5% of *K. pneumoniae* isolates were resistant to carbapenems. The mentioned figures are on par with the outcomes from South India that were reported by Nagaraj et al. (2012) [12], who found out the resistance rates about 36-42% for both *E. coli* and K. pneumoniae. Nevertheless, the resistance in this study is higher than that of the preceding Indian studies, which indicated a range from 5.75% to 25% for carbapenem resistance during surveillance, reflecting a trend up over (Gupta et al., 2011) [13]. This increase could be due to the higher consumption of carbapenems, longer hospitalization, and poor antimicrobial management.

According to phenotypic detection, 79.49% of carbapenem-resistant isolates tested positive by the Modified Hodge Test (MHT) and, on the other hand, 84.61% were recognized as metallo-β-lactamase (MBL) producers through disk potentiation testing. Deshmukh et al. (2011) [14] have reported similar MBL production rates, which were ranging from 70% to 85%. In contrast, reports from certain areas indicated MHT sensitivity to be lower, especially for NDM producers, which pointed at the drawbacks of’ this technique (Sahin et al., 2015). The fairly high detection ‘rate of MBL in our research indicates that MBLs are the main playing factor when it comes to carbapenem resistance in this region.

Genotypic analysis revealed that the blaNDM gene was found in 84.61% of the carbapenem-resistant isolates, whereas blaKPC was absent. Similar to reports from the Indian subcontinent, where the blaNDM gene has been the main carbapenemase gene (Kumarasamy et al., 2010) [15] the present findings corroborate the results. On the other hand, the U.S. and parts of Europe studies consider blaKPC as the predominant carbapenemase, which emphasizes an extreme difference between geographical resistance mechanisms (Nordmann, 2014) [16]. The finding of no blaKPC in our study reinforces the idea that the clonal spread of resistance organisms and the local use of antibiotics strongly determine the incidence of different types of carbapenemase in a given region.

The patterns of antimicrobial susceptibility found in this study underline the clinical significance of these findings even more. The two bacteria showed a significant degree of resistance to the third generation of cephalosporins and fluorquinolones, in line with worldwide reports about the presence of ESBLs among most resistant strains (Paterson & Bonomo, 2005). With aminoglycosides (antibiotic drugs that work by inhibiting the growth of bacteria), though their use was limited, susceptibility was seen in a little over half of *E. coli* isolates which is a finding similar to Sahin et al. (2015) study. On the other hand, reduced aminoglycoside sensitivity among *K. pneumoniae* in

the present study is in contrast with previous reports that recorded better preservation of aminoglycoside activity and suggested the increasing acquisition of resistance determinants.

The presence of' blaNDM-positive isolates in large numbers is alarming specially because of the gene's plasmid-mediated character which allows its 'transfer across species very fast (Kumarasamy et al., 2010). Enterobacterales are considered as minor components of gut flora but they serve as the main supporting causes for the resistance genes which in turn lead to the silent proliferation of these genes within healthcare establishments (Nagaraj et al., 2012). The combined factors of this reservoir potential and poor infection control measures probably lead to the resistance rates observed.

In general, the current investigation as an example, together with the literature, confirms that the carbapenem resistance caused mainly by NDM-type carbapenemases is becoming increasingly prevalent. The resistance rates seen here are indicative of a deteriorating situation as compared to previous studies conducted in India. This necessity for the implementation of phenotypic and genotypic surveillance as routine practices, detecting the producers of carbapenemases at an early point, rational use of antibiotics and among others, strict infection control measures are highlighted. The progress of potent antimicrobial stewardship programs will be crucial in subsiding the further dispersal and safeguarding the remaining therapeutic alternatives.

CONCLUSION

A tertiary hospital setting has been shown through this research to have a considerable amount of' carbapenem-resistant *Escherichia coli* and *Klebsiella pneumoniae* strains, with urine as the main isolate source. The two pathogens showed very wide multidrug resistance that included carbapenems, cephalosporins, and fluoroquinolones having uncommonly low susceptibility that resulted in very few treatment options left. Phenotypic testing showed that there was a lot of carbapenemase and metallo-β-lactamase production, whereas genotypic analysis pointed out blaNDM as the main resistance gene, thus, it was implied that the gene has a major role in local resistance epidemiology. The presence of several resistance mechanisms in some isolates made the treatment even more difficult. These results indicate that it is very important to use both phenotypic and molecular diagnostic approaches integration for early detection, hold infection control practices, and develop strong antimicrobial stewardship programs in order to combat the spread of carbapenem-resistant pathogens and keep the remaining effective antibiotics.

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