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PREVALENCE OF CARBAPENEM RESISTANCE IN ESCHERICHIA COLI ISOLATES AT A TERTIARY CARE INSTITUTE IN NORTH WEST REGION OF RAJASTHAN

Medical Microbiology

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ABSTRACT

Introduction: The emergence and spread of carbapenem-resistant Escherichia coli (E. coli) pose a serious threat to human health worldwide. This study aimed to investigate the phenotypic detection underlying carbapenem resistance and their prevalence among E. Coli. Isolates.

Material and methods: The current study as carried out at a tertiary care institute in North West region of Rajasthan, from Aug 2018 to Jan 2021. The test group selected was the population of patients from OPD & IPD of P.B.M hospital. All participants completed a medical history form and provided informed consent. Total 213 E.coli isolates were taken irrespective of age, sex, occupation, religion and ethnicity for Carbapenemes resistance in from various clinical samples i.e urine, pus/wound swab, blood, CSF and respiratory secretion received in microbiology laboratory.

Results: It is observed that the total of 213 isolates of E. coli from 1050 patients were included in this study. About 71.36% (n = 152) of the patients were males and the median age of the patients was 65 years. The rate of carbapenem resistance was significantly higher in males as compared to females 28.64% (n=61) ($p < 0.001$). Carbapenem resistance rate was significantly higher in the inpatients 87.32% (n=186) than outpatients 12.67% (n=27) ($p < 0.0001$) is detailed in Table I. Most of E.coli Isolates were obtained from urine samples (53.52%), followed by Blood (15.96%) , pus and sputum (8.92%) revealed.

Conclusion: The emergence of Carbapenem Resistance in Escherichia has become major public health issue. Early detection of changing resistance patterns is very important in preventing the dissemination of resistant bacteria and modifying the treatment strategies.

KEYWORDS

Carbapenem Resistance, *Escherichia coli*

INTRODUCTION

The high prevalence of carbapenem resistant is a growing public issue worldwide. *Escherichia coli* is one of the most common causative agents of a wide range of clinical infections varying from meningitis, urinary tract infections, and sepsis. Carbapenems are the only antibiotic option left for the treatment of infections caused by multidrug-resistant *E. coli*. However, the emergence of carbapenem resistance leads to the failure of empirical therapy with carbapenems. [1-3]

Escherichia coli (*E. coli*) is the most versatile known microorganism [1]. It is a common commensal of gastrointestinal tract of human and animal. Also, it comprises pathogenic strains divided into intestinal or diarrhoeagenic *E. coli* (DEC) and extraintestinal pathogenic *E. Coli* (ExPEC). The main infections caused by ExPEC are urinary tract infections (UTIs), sepsis, meningitis, and wound infections [2–4]. A large proportion of humans are affected by UTIs, with annual prevalence of about 150 million cases. Yearly, $5 billion are spent for treatment of UTIs in the USA with estimated cases of 11 million per year [5]. Uropathogenic *E. coli* is the most prevalent ExPEC and it is the primary cause of UTIs all over the world [3]. Uropathogenic *E. coli* strains have a wide variety of virulence factors which include: immune suppressors, adhesins (fimbrial and afimbrial adhesins), siderophore systems, the serum resistance, the capsular polysaccharide K antigen, and toxins [3, 5].

Carbapenems emerged as bactericidal β-lactam antimicrobials with confirmed activity in severe infections caused by extended spectrum β-lactamases (ESBLs) producers [6]. These antimicrobials have broad spectrum antibacterial activity and have a unique structure that is composed of a carbapenem linked to a β-lactam ring which provides protection against most β lactamases such as metallo-β-lactamases (MBLs) and ESBLs [7]. Therefore; carbapenems are considered one of the most reliable drugs for treating bacterial infections and the occurrence and distribution of resistance to them constitute a major public health problem [8]. There are three possible mechanisms for carbapenems resistance in the family Enterobacteriaceae. These are: efflux pump overactivity, porin loss or mutation, and carbapenemase production, which is the main mechanism of resistance to these antimicrobials [9–11]. Carbapenemases are enzymes (β-lactamases) that are encoded by both chromosomal and plasmid-mediated genes and structurally belonging to different Ambler classes (A, B, and D). These enzymes can hydrolyze a broad range of β-lactams, including carbapenems, cephalosporins, penicillin, and aztreonam. Also, bacterial strains possessing carbapenemases are often resistant to multiple drugs (MDR) [11]. Carbapenemases are the major mechanisms of resistance, and carbapenemase harboring isolates have been reported from across the globe with varying rates of prevalence. Globally, Klebsiella pneumoniae carbapenemase (KPC) is the most common carbapenemase, while in the Indian subcontinent, New Delhi metallo-β-lactamase (NDM), which supposedly originated in India in 2008, is the most commonly reported carbapenemase [12-14]. Various variants of NDM differing from each other in one or few nucleotides have emerged over the years [15]. Besides NDM, oxacillinase-48 (OXA-48)-like enzymes have also been reported from India [16]. In India, NDM has spread to community and has been reported from public tap water and sewage isolates [17]. Escherichia coli and Klebsiella pneumoniae are the most common Gramnegative pathogens in clinical microbiology laboratories, and the resistance rate to carbapenems in these organisms is high in India [18]. The rise in antimicrobial resistance poses a serious challenge in centers where international patients come for treatment. This study was undertaken in a Govt. hospital in North-West Rajasthan, India that caters to both Indian and international patients with the aim to find out the prevalence of important carbapenemases in E. coli.

MATERIAL AND METHODS

Study design, bacterial isolates, and patient profile

The current observational study as carried out at a tertiary care institute in North West region of Rajasthan, from Aug 2018 to Jan 2021. The test group selected was the population of patients from OPD & IPD of P.B.M hospital. All participants completed a medical history form and provided informed consent. Total 213 E.coli isolates were taken irrespective of age, sex, occupation, religion and ethnicity for Carbapenemes resistance in from various clinical samples i.e urine, pus/wound swab, blood, CSF and respiratory secretion received in microbiology laboratory. The study design was approved by the institutional ethics committee. The study protocol was reviewed and approved by the research cell of Rajasthan University of Health Sciences and Ethical approval was also obtained from the Ethics committee.

LABORATORY DIAGNOSIS:

The samples received in the laboratory were processed in the following manner

INCLUSION CRITERIA:
All consecutive, non-duplicate isolates of Escherichia coli collected from various specimens of patients attending various outpatient departments as well as admitted in wards at P.B.M hospital from Aug, 2018 to Jan, 2021. All kind of specimens like urine, blood, pus, wound and respiratory tract specimen, body fluid, high vaginal swab, swab from non healing ulcers and CSF were included in the study.

EXCLUSION CRITERIA:
Isolation of three organism types with no predominating organism and repeated isolate from same patients were excluded from this study.

STUDY PROTOCOL
Sample Processing: All samples except blood were cultured on Blood agar and MacConkey's agar and Thioglycolate broth. Blood was culture on Brain heart infusion broth. Urine was cultured on Blood & MacConkey's agar. A culture plates were incubated overnight at 37ºC. Identification of organisms was done on the basis of, Gram's staining, motility, colony characteristics and biochemical confirmation tests.

Detection of Carbapenem drug resistance by phenotypic methods
1. Imipenem Resistance by Disc Diffusion test-
Routine antibiotic susceptibilities were determined by the CLSI disc diffusion assay and interpreted using CLSI breakpoints as per CLSI guidelines. Plates of Mueller-Hinton agar were inoculated with suspensions of the E.coli strains and adjusted to turbidity equivalent to 0.5 McFarland standards. A set of discs of IPM and MRP, (10 µg each) was applied to the surface of the agar, plates were incubated overnight at 37°C in Incubation, and diameters of zones of inhibition were recorded less than 19 mm zone were considered as Imipenem resistant. E.coli ATCC 25922 were used for Quality control

1. Imipenem and Imipenem+EDTA combined disc test:
Suspensions of the test strain,(opacity adjusted to 0.5 McFarland opacity standards) was used to inoculate a plate of Mueller -Hinton agar .After drying ,two disc 10 µg imipenem and imipenem with EDTA disc (10/750µg) were placed 20 mm apart from center to center. After overnight incubation, if the increase in inhibition zone with the imipenem and EDTA disc was ≥7 mm, then with the imipenem disc alone, it was considered as MBL positive. E.coli ATCC 25922 were used for Quality control.

2.Modified Hodge Test: A 1/10 dilution of 0.5 McFarland turbidity standard of fresh overnight growth of the indicator organism Escherichia coli ATCC 25922 was inoculated on Mueller Hinton agar and allowed to dry for 3-5 minutes. A 10 µg Meropenem/ 10µg Ertapenem. disc was placed in the center of the test area. In a straight line, test organisms were streaked from the edge of the disk to the edge of the plate. Up to four organisms can be tested on the same plate with one drug. This was incubated overnight at 37^0C. After overnight incubation the plate was examined for a clover leaf type indentation at the intersection of the test organism. Klebsiella pneumoniae ATCC BAA-1705 were used for Positive control. Klebsiella pneumoniae ATCC BAA-1706 were used for Negative control.

3. MBL detection by Imipenem / Imipenem E Strip
1. Plates were prepared with suitable make of Mueller Hinton Agar.
2. a sterile non-toxic cotton swab on a wooden applicator was dipped into the standardized inoculum and soaked swab was rotated firmly against the upper inside wall of the tube to express excess fluid. entire agar surface of the plate was streaked with the swab three times, turning the plate at 60° angle between each streaking.
3. Applicator was hold in the middle and gently press its broader sticky side on the centre of Ezy MIC™ strip.
4. The strip was placed at a desired position on agar plate swabbed with test culture. Gently turn the applicator clockwise with fingers. With this action, the applicator was detached from the strip.
5. Plates were transferred in the incubator under appropriate conditions. E.coli ATCC 25922 was used for Quality control.

STATISTICALANALYSIS
Detailed data of all subjects of case and control group were collected. After complete evaluation all findings were expressed in terms of Mean ± SD. Comparison between case group and control group was done using paired "t" test. All statistical analysis was done using SPSS software version 20. A statistical value of $p<0.05$ was considered significant.

RESULTS
A total of 213 isolates of E. coli from 1050 patients were included in this study. About 71.36% (n = 152) of the patients were males and the median age of the patients was 65 years. Bacterial identification of these clinical samples done by culture on Blood agar and Mac Conkey's Agar. Biochemical Identification was done using Indole test, Methyl red test, Citrate Utilization test, Urease Hydrolysis test, and Triple sugar iron test (TSI).The rate of carbapenem resistance was significantly higher in males as compared to females 28.64% (n=61) ($p < 0.001$). Carbapenem resistance rate was significantly higher in the inpatients 87.32% (n=186) than outpatients 12.67% (n=27) ($p < 0.0001$) is detailed in Table I. Most of E.coli Isolates were obtained from urine samples (53.52%), followed by Blood (15.96%) , pus and sputum (8.92%) each observed in Table II. The table III shows that the distribution of patients in various wards was found to maximum number of E.coli. isolated from ICU (31.92%) followed by Urology ward (20.65%). The Correlation between Risk Factor associated among various clinical patients from which E.coli isolates obtained in table IV. Out of 213 isolates of E.coli was isolated from patient with risk factors. It was observed that maximum number of E.coli were isolated from the patient had Prolong hospital stay 29.1% followed by CKD cases (20.65%) and UTI (15.96%).

OBSERVATION TABLES

Table – 1 Demographic Characteristics Of Patients (n=213) With No. Of E.coli Isolated

Characteristics	No. of E.coli Isolated (N=213)	Frequency (100%)
Gender		
Male	152	71.36%
Female	61	28.64%
Age (Years)		
0-10	13	6.10%
11-20	13	6.10%
21-30	31	14.55%
31-40	32	15.02%
41-50	35	16.43%
51-60	29	13.61%
61-70	46	21.59%
71-80	14	6.57%
Out Door/In Door		
OPD	27	12.67%
IPD	186	87.32%

Table 2: Distribution of E.coli Isolated from various clinical samples

Specimen	No. of E.coli Isolated (N=213)	Frequency (100%)
Pus	19	8.92%
Sputum	19	8.92%
Urine	114	53.52%
Blood	34	15.96%
Pleural Fluid	12	5.63%
BAL Fluid	2	0.93%
Synovial Fluid	3	1.40%
CSF	7	3.28%
Ascitic Fluid	3	1.40%

Table 3: Ward Wise Distribution of *E.coli* in Various Clinical Samples

WARD	*E.coli* isolates	Percentage
ORTHO Ward	3	1.40%
Pediatric Ward	9	4.22%
Medicine Ward	30	14.08%
Urology Ward	44	20.65%
Surgery Ward	22	10.32%
GI Ward	3	1.40%
ENT Ward	4	1.87%
Obs & Gynae Ward	3	1.40%
ICU	68	**31.92%**
OPD	27	12.67%

Table 4: Correlation between Risk Factor associated among various clinical patients from which E.coli isolates obtained

Risk Factors	No. of Isolates of *E.Coli*	Percentage
Prolong hospital stay	62	29.10 %
Chronic Obstructive Pulmonary Disorder	7	3.28 %
Diabetic	20	9.38 %

GI Cancer	2	0.93 %
Chronic Kidney Disease	44	20.65%
Joint Replacement	2	0.93 %
UTI	34	15.96 %
CA-UTI	8	3.75 %
Meningitis	4	1.87 %
Sepsis	18	8.45 %
Trauma	12	5.63 %

DISCUSSION

Antibiotic resistance is a public health menace in India and the rate of carbapenem resistance is also showing an alarmingly increasing trend [19].

Antibiotic resistant bacteria appear to be biologically fit and capable of causing serious life threatening infections. The increase in antibiotic resistance among gram-negative bacteria, such as Enterobacteriaceae group is a notable example of how bacteria can procure, maintain and express new genetic information that can confer resistance to one or several antibiotics. Resistance in gram-negative bacteria is a serious problem and calls for an effective infection control measures to curb their dissemination [20].

In the present study, there was a male predominance (71.36%) among the patients from whom isolates were obtained. It was observed that males are more affected as compared to female. It was because most of samples were received from Urology ward from male patients. Similar types of studies have been carried out in the past. Nagoba and Wadher have reported more number of males (53.17%) than females (46.82%). In another study by Shobha et al. also more number of males (54.37%) than females (45.62%) have been reported. Ahmad et al. also reported more number of males (76.17%) than females (23.83%) [21-24].

In the current study, The maximum number of isolates were from the patients in the age group of 61-70 yrs (21.59%) followed by (16.43%) age group of 41-50 yrs and (15.02%) at 31-40 yrs. The age-wise distribution of E.coli isolates in particular has rarely been reported. However, age-wise distribution of infections in general has been reported in some of the studies. Nagoba and Wadher reported maximum E.coli isolates (79.31%) in the age group of 41-50 years while minimum E.coli isolates in the age group 0-10 years . Mansour Amin et al reported maximum E.coli isolation rate in between 21-40 years of age group. Babu *et al.* reported maximum E.coli isolation rate in the age group of 21-40 years. Our finding of maximum E.coli isolation rate in the age group 61-70 years is similar to the finding of Ahmed *et al.*[16]. It was not in an agreement with Nagoba and Wadher, Banerjee and Babu et al. [25-28].

In the present study, Out of 213 E.coli isolates, maximum E.coli were isolated from urine samples (53.52%), followed by Blood (15.96%) , pus and sputum (8.92%) each. Our findings of urine as a most common specimen yielding E.coli followed by blood fairly correlates with Agarwal et al. Aggarwal et al reported an isolation rate of E.coli from urine 50%, Shaswati et al reported 65.32% and Rudresh et al reported 33.1%.In the current study, maximum number of E.coli. were isolated from ICU (31.92%) followed by Urology ward (20.65%). In a National Surveillance Programme, it has been found that gram-negative bacteria are commonly associated with various infections in patients admitted in ICUs (108).Aziz Japoni et al also reported 28.7% E.coli isolates from ICU patients. Out of 213 isolates of E.coli were isolated from the patients with some underlying risk factors. It was observed that maximum number of E.coli were isolated from the patient with prolonged hospital stay 29.1%, followed by CKD cases (20.65%) and UTI (15.96%). RonenBen-Ami et al(139) also maximum number of E.coli isolates from hospitalized patients.. Nakai Hazuki et al. in a multivariate analysis identified cerebrovascular disease, intubation and major surgery as a risk factor for E.coli infection. [29].

In the current study Out of total 213 E.coli isolates, 56 (26.29%) were carbapenem resistant E.coli. Our study was in agreement with other studies- ie R.A. Dahab et al who reported 25.41% CRE in sudan, Hossein Kazemain et al. reported 27.7% carbapenem resistant E.coli in Iran and Namita Jaggi et al. reported 29.4% CRE in Haryana. Varaiya et al. reported a prevalence rate of 26%. howeve Muley et al. reported 35% isolates resistant to carbapenems which are higher than our finding . A prevalence rate of 20.31% has been reported by Dwivedi et al. Bashir et al. reported 13.42%. which are lower as compared to our study. [30-34].This baseline data generated from this study in a tertiary hospital is important in view of the growing antibiotic resistance and flourishing medical tourism.

CONCLUSIONS

The emergence of Carbapenem Resistance in Escherichia has become major public health issue. Early detection of changing resistance patterns is very important in preventing the dissemination of resistant bacteria and modifying the treatment strategies. For infections caused by Carbapenem resistant E.coli therapeutic options are limited. The implementation of simple and accurate laboratory method to detect carbapenemes producing E.coli production is useful; our study high lights the carbapenem resistance among E.coli isolated from OPD & IPD units and especially from intensive care unit, indicates that widespread use of those antibiotics that leads to selection of resistant organisms. In present study the detection of carbapenem resistant E.coli is done by phenotypic method. The situation is alarming because there are very few therapeutic options available in the near future for these multidrug-resistant organisms. Additionally, Phenotypic methods would serve as a better tool for the identification of these Carbapenem Resistance.Further study required to help early detection, isolation and contact precaution of of Carbapenem Resistance in Escherichia for prevention and treatment modalities.

DISCLOSURE STATEMENT

This study is investigator initiated. The authors declare that they have no competing/conflict of interests in relation to this article.

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CONSENT FOR PUBLICATION

- Not applicable.
- Ethics approval and consent to participate.
- The study protocol was approved by the medical ethics committee of the Rajasthan University of Health Sciences, Jaipur, Rajasthan (State), India.

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