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ANTIBIOTIC SUSCEPTIBILITY PATTERN OF CARBAPENEM RESISTANT ENTEROBACTERIACEAE AMONG UROPATHOGENS ISOLATED IN A REFERRAL LABORATORY OF KARACHI

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ABSTRACT

Objective: To determine the antibiotic susceptibility pattern of Carbapenem resistant Enterobacteriaceae among uropathogens isolated in a referral laboratory in Karachi.

Methodology: It is a retrospective cross-sectional study, carried out at the Department of Microbiology of Dow Diagnostic Research and Reference Laboratory. All urine samples collected during the study period of 6 months from October 2020 to March 2021 were tested for culture and sensitivity patterns by the disc diffusion method. Data of urine culture and sensitivity test reports were taken from the medical record. and analyzed by using SPSS version 16.

Results: Out of the total 10925 uropathogens isolated, 67% belonged to Enterobacteriaceae family. The most frequent isolate among them was Escherichia coli 84% followed by Klebsiella species at 10%. The overall prevalence of Carbapenem resistance was 6%. The frequency of Carbapenem resistance was higher in Klebsiella species 27% than Escherichia coli 8%. Multi-drug resistance was observed in both Escherichia coli and Klebsiella species especially against Ampicillin, followed by Cefixime, Cefuroxime, Ceftriaxone, Cotrimoxazole and Ciprofloxacin.

Conclusion: The study showed a significant rate of Carbapenem resistance among Enterobacteriaceae which emphasizes the need for formulating an antimicrobial policy with its strict implementation and regular surveillance to control the spread of Carbapenem resistant Enterobacteriaceae at the hospital and community level.

Keywords: Carbapenem; Enterobacteriaceae; Escherichia coli; Resistance

INTRODUCTION

A Urinary Tract Infection (UTI) is considered one of the most prevailing bacterial infections after the upper respiratory tract infection. It is often associated with prolonged hospital stay and increased mortality rate due to septicemia. Every year, 150 million people develop UTI globally costing health care an approximate of 6 billion dollars.[1] Gram negative bacteria, especially the family of Enterobacteriaceae, are the most predominant cause of both Nosocomial and community acquired UTIs. They have developed a multidrug resistance to both the first and second line of antimicrobials.[2]

Earlier, one of the main causes of development of resistance in Enterobacteriaceae was the production of antibiotic degrading enzymes, like pencillinases, cephalosorinases, and extended spectrum ß-lactamase (ESBL). Currently the last antibiotic option available to treat ESBL producing Enterobacteriaceae is a Carbapenem group of ß-lactam antibiotics including meropenem, imipenem, ertapenem, & doripenem.[3,4] However, production of carbapenemase hydrolyting enzymes, coded by blaKPC, blaVIM and blaIMP, has further increased resistance among Enterobacteriaceae.[5] In United Kingdom, a new metallo-ß–lactamase was identified as New Delhi metallo-ß-lactamase (blaNDM) in clinical isolates of Escherichia coli (E. coli) and Klebsiella pneumonia in a Swedish patient who visited India.[6] Other studies have also reported similar resistance gene which have posed high level of resistance to the available antimicrobials, making them ineffective in treating infections. It can eventually result in an increased risk to the public health by spreading resistance widely and causing high mortality rates. Literature shows that amongst Enterobacteriaceae, the most common isolates with Carbapenem resistance were E. coli and Klebsiella species (sp.).[7] Patients who are on invasive devices like intravenous catheter, urinary catheters, nasogastric tubes or ventilators as well as those suffering from recurrent infections and taking antibiotics for a long period of time are key victims of Carbapenem resistant Enterobacteriaceae (CRE).[8]

While understanding the magnitude of the problem, there is a need to have updated information regarding prevalence and antimicrobial susceptibility pattern of the Enterobacteriaceae in urinary isolates for appropriate empirical therapy of urinary tract infection. Therefore, this study was designed to determine prevalence and antibiotic susceptibility pattern of Enterobacteriaceae isolated from urinary tract infected patients.

METHODOLOGY

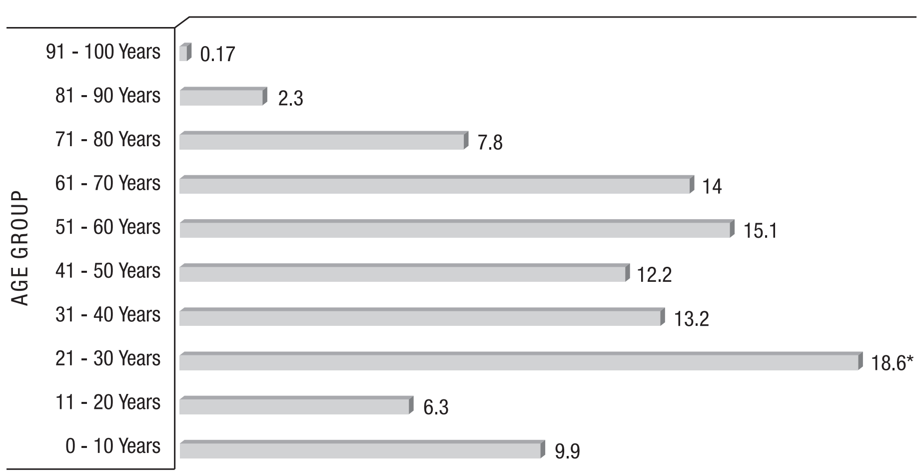
This retrospective, cross-sectional study was conducted at the Department of Microbiology Dow Diagnostic Research and Reference Laboratory (DDRRL). The data of urine and culture sensitivity test report was collected from the medical record of Microbiology section after getting approval from Institutional Review Board (IRB) with Reference No. IRB-1794/DUHS/Approval/2021. The culture reports included samples from both inpatient and outpatient department during a period of six months from October 2020 to March 2021. A sample size of 28,505 subjects was taken, that have achieved more than 99% power to detect a marginal error of 5%, a 95% confidence interval, and an 84% prevalence of E. coli using PASS version 15 software. A one-sample test was used to calculate proportion. The same power of the study was taken for Klebsiella sp. with a 10% prevalence. Each report has data of patient's age, gender, isolated organism and its antibiotic susceptibility pattern. Culture reports having complete information regarding patient's age, gender, and isolated organism were included in the study. Moreover antibiotic susceptibility pattern of only gram negative bacteria belonging to the family of Enterobactericeae were included in the study. . Culture reports having a lack of above mentioned in a patient's information were excluded from the study. The antibiotic susceptibility pattern of organisms other than family of Enterobacteriaceae were excluded as well. In Microbiology lab, urine samples were processed according to standard microbiological procedures and antibiotic susceptibility test was performed as stated in CLSI guidelines 2021.(9) The antibiotic discs used for susceptibility testing of gram negative bacteria of family Enterobacteriaceae included Ampicillin 10µg, Amoxicillin / Clavulanic acid 30µg, Piperacillin / Tazobactam 110µg, Amikacin 30µg, Meropenem 10µg, Gentamicin 10µg, Cefixime 5µg Ceftriaxone 30µg, Cefuroxime 30µg, Ciprofloxacin 5µg, Cotrimaxazole 25µg, Nitrofurantoin 300µg and Fosfomycin 200µg. The entire data was entered in SPSS version 16 and descriptive statistics was measured in percentages. Further statistical analysis was done by using cross tab to compare frequency of uropathogens with age groups and also to compare sensitivity pattern of uropathogens against antibiotics.

RESULTS

In this study, a total 28,505 urine cultures and sensitivity test report data was taken from medical record of a period of 6 months from October 2020 to March 2021. Out of these, 10,925 (38%) showed positive bacterial growth having a female to male ratio of 2.6:1. Amongst these, 7,849 (72%) of specimens belonged to female patients and 3,076 (28%) of specimens were of male patients with overall mean age of the patient found to be 42.5 years. Significant bacterial growth was found much higher in the patients having age ranging between 21-30 years followed by 51-60 years in comparison to other age groups. (Figure-I).

Out of the total 10,925 uropathogens isolated, 67% (7,285) belonged to Enterobacteriaceae family. The most frequent isolate among them was E. coli 6,135 (84%) followed by Klebsiella sp. 704 (10%). (Figure- II)

Antibiotic sensitivity pattern of only E. coli and Klebsiella sp. were analyzed as other



* Showing high percentage of uropathogens in age groups

Figure 1: Age group wise distribution of isolated uropathogens in %

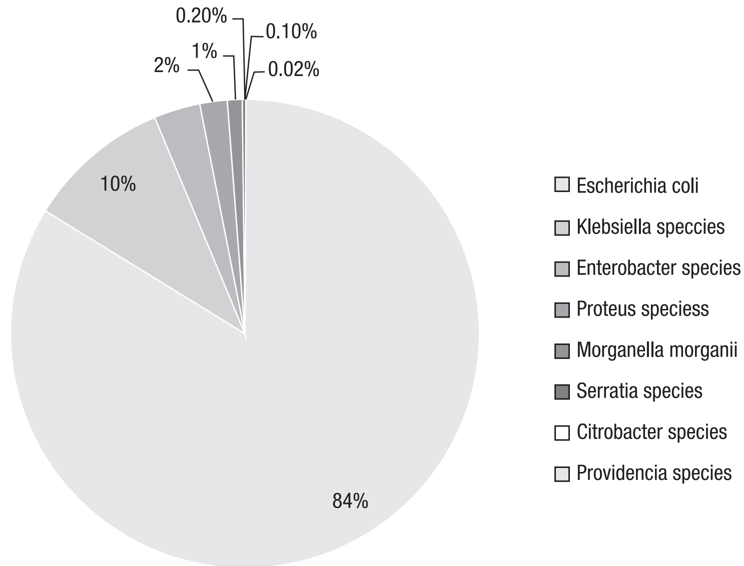


Figure 2: Frequency of isolated Enterobacteriaceae in %

Table 1: Antibiotic resistance pattern of isolated Enterobacteriaceae

Antibiotics	Escherichia coli N= 84% (6,135)	Klebsiella sp. N= 10% (704)
Ampicillin	5276 (86%)*	-
Amoxicillin / Clavulanic acid	2024 (33%)	190 (27%)
Piperacillin / Tazobactam	613 (10%)	105 (15%)
Ceftriaxone	4171 (68%)*	282 (40%)
Cefixime	4539 (74%)*	330 (47%)*
Cefuroxime	4539 (74%)*	330 (47%)*
Meropenem	491(8%)	190(27%)
Gentamicin	1533 (25%)	133 (19%)
Amikacin	122 (2%)	77 (11%)
Ciprofloxacin	3865 (63%)*	211(30%)
Cotrimoxazole	4171 (68%)*	295 (42%)*
Fosfomycin	491 (8%)	77 (11%)
Nitrofurantoin	306 (5%)	147 (21%)

*Microorganisms showing increased resistance to antibiotics, - Antibiotics not tested

members of Enterobacteriaceae isolated were in very less number. Therefore, a total of 6,839 Enterobacteriaceae isolates (E. coli 6,135 & Klebsiella sp. 704) were analyzed for antibiotic sensitivity pattern. Overall prevalence of Carbapenem resistance among them was 6% (390/ 6,839). The frequency of Carbapenem resistance was higher in Klebsiella sp. 190 (27%) than E. coli 491 (8%). Most sensitive antibiotics to E. coli were Amikacin 98 %, Nitrofurantoin 95%, Meropenem 92%, Fosfomycin 92% and Tazobactam 90% respectively. However, the most sensitive antibiotics to Klebsiella sp. were Amikacin 89%, Fosfomycin 89% and Tazobactam 85% respectively. (Table-I).

DISCUSSION

This study emphasized on the frequency of Carbapenem resistant Enterobacteriaceae (CRE) among urinary isolates which has become an emerging threat to public health. Statistical analysis of the data showed a frequency of 6% CRE in this study. Similar results were observed in Nigeria by Suwaiba M. et al.[10] and in North India by P Datta et al.[11] However, a high prevalence of CRE was reported by Gurung S. et al[12] and Wattal C et al[13] in Nepal and Delhi respectively.

Further in this study, a higher rate of Carbapenem resistance (CR) was noticed in Klebsiella sp. 27% than in E. coli 8%. Similar findings were found in studies conducted by Shields R.K. et al[14] and Matar et al.[15] In contrast, in Mumbai, Nirangan et al reported a higher prevalence of CR in E. coli 49.8% than in K. pneumonia 37.4%.[16] Research studies showed that factors causing an increased CR in gram negative bacteria include production of carbapenemase enzymes, loss of porin proteins, increased expression of efflux pumps and modification in penicillin binding proteins.[17]

Moreover, it has been observed that the prevalence of CRE in different studies is distinct from each other which can be due to the difference in consumption of Carbapenem and other antibiotics in those geographical areas and study population.

It is necessary to implement antimicrobial stewardship in all health care centers by reserving broad spectrum antimicrobial agents and using them only when it is highly recommended.[18] As shown in multiple research reports, CRE have rapidly increased in number within the last few years, which is an alarming threat for the health care sector. It can become the source of a nation-wide surge of healthcare associated infections in near future. The lack of any infection control plan in the health care system to limit the spread of CR can result in a very devastating situation for public health.

According to the World Health Organization report of 2014,[19] ample data on the prevalence of CPE is not available in developing countries. Therefore, it has been emphasized in the report to conduct surveillance programs in these countries on a regular basis to identify the magnitude of resistance strains in these areas.

CONCLUSION

Multi-drug resistance has been observed in both Klebsiella sp. and E. coli especially against Ampicillin, followed by Cefixime, Cefuroxime, Ceftriaxone, Cotrimoxazole and Ciprofloxacin. Moreover, the overall prevalence of CRE was found to be 6%, with a higher percentage of resistance in Klebsiella sp. was 27% than 8% in E. coli. Local surveillance programs should be established on regular basis to identify and monitor emergence of antibiotics resistance. In-depth knowledge of the prevalence and resistance pattern of CPE may help infection control team to take necessary actions to combat widespread dissemination of CRE.

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Author's Contribution

SN Performed the data analysis and interpretation of data. AF contributed in the literature search and helped in the analysis of data. FF, SI, and HG contributed in data collection and drafted the manuscript for final approval. FZ conceived the idea and helped in the write-up of the manuscript. Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest

Authors declared no conflict of interest

Grant Support and Financial Disclosure

None

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.