The Professional Medical Journal
www.theprofesional.com

ORIGINAL PROF-0-3854

DOI: 10.29309/TPMJ/2020.27.2.3854

MULTIDRUG-RESISTANT URINARY TRACT ISOLATES OF ESCHERICHIA COLI: FREQUENCY AND PATIENT DEMOGRAPHICS IN A TERTIARY CARE HOSPITAL.

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Article received on:
25/06/2019
Accepted for publication:
15/09/2019

ABSTRACT: Urinary tract infections (UTIs) are a major burden to the health care as it is estimated that around 150 million UTIs occur yearly worldwide. Enterobacteriaceae are the most common agent causing serious urinary tract infections; and multi drug resistent (MDR) cases are increasing day by day. **Objectives:** To determine the frequency and patient demographics of multidrug resistant urinary tract isolates of Escherichia Coli in a Tertiary Care Hospital. **Study Design:** Retrospective cross sectional study. **Setting:** Department of Medicine, Madinah Teaching Hospital / The University of Faisalabad, Faisalabad. **Period:** May 2016 to Sep 2018. **Material & Methods:** 187 patients of age 15 to 90 years with positive E. coli on urine culture and sensitivity were included in this retrospective cross sectional study. All those patients with history of dysuria (pain during urination) or frequent urination (more than 7 times per day) were advised urine complete analysis and those with >5 WBCs or pus cells /HPF or having positive for leukocyte esterase and/or nitrite, were advised urine culture and sensitivity. Main outcome variable was the frequency of MDR cases among the culture positive E. coli UTI patients. **Results:** Among all the cases of E. coli UTI, frequency of MDRE UTI was 66.8% (n=125) and rest 33.2% (n= 62) cases were not MDR UTI. 97.3% patients were resistant to lactam antibiotics, 95.7% were resistant to quinolones and 68.4% were resistant to aminoglycosides. **Conclusion:** With the rise in the microbe's resistance to multiple drugs, new therapeutic strategies are to be designed after analyzing our population's susceptibility pattern. It is not less than a challenge for physicians of a developing nation like Pakistan to treat MDR E.coli UTI cases while taking care of the cost of treatment and controlling the disease burden at the same time.

Key words: Cystitis, E. Coli, Gram Negative, MDR, Muti-drug Resistance, UTI, Urine Infection, Urine Culture.

Article Citation: Azhar S, Baig MW, Rasool S, Khan RR, Munir T, Fatima U, Ahsan M. Multidrug-resistant urinary tract isolates of escherichia coli: Frequency and patient demographics in a Tertiary Care Hospital. Professional Med J 2020; 27(2):335-340. **DOI:** 10.29309/TPMJ/2020.27.2.3854

INTRODUCTION

Urinary tract infections (UTIs) are a major burden to the health care as it is estimated that around 150 million UTIs occur yearly worldwide.[1] Urinary tract infection (UTI) is the fourth most common bacterial infection encountered by the physicians, occurring in all age groups and affecting both genders. About 20% of these infections occur due to gram positive microbes and more than 80% by gram negative microbes.[2,3]

Enterobacteriaceae are the most common agents causing serious urinary tract infections. These infections are also prevalent in Pakistan but with the development of antimicrobial resistance, MDR cases are increasing day by day. Choice of antimicrobial for treatment depends on the susceptibility profiles of the Enterobacteriaceae.[4] As recommended by the Infectious Diseases Society of America, factors like local data of antimicrobial resistance, availability of antimicrobial under consideration and patient's history of drug allergies and tolerability profile should be kept under consideration.[5]

Nitrofurantoin or trimethoprim-sulfamethoxazole can be used for uncomplicated cystitis patients and quinolones, ceftriaxone, aminoglycosides, and carbapenems can be given as the empirical antimicrobial treatment for pyelonephritis/ complex UTIs. With the rise in multidrug-resistant Enterobacteriaceae (MDRE), choice of

antimicrobial has become a challenge for the treating physicians.[6]

Previously, resistance was reported for extended-spectrum beta-lactamases, now ending up in MDRE.[7] It has been reported that antibiotic resistance varies directly with the antibiotic abuse[8], and MDR microbes are on the rise because of the excessive use of antimicrobials prescribed without investigating the nature and cause of disease, thus abusing them.[9,10] Appropriate and prompt antimicrobial treatment of MDRE cases should be done to decrease morbidity and mortality.[11]

Prevalence of UTI is 11.6% among symptomatic patients in Pakistan, with trend approximately twice as high in females than males; and 80% of these are caused by gram negative rods (E.Coli UTI in 41% cases).[12] As, limited local studies are available on the MDR E. coli urinary tract isolates[13], the objective of our study was to determine the frequency and demographics of MDR E. coli urinary tract isolates among patient presenting in a tertiary care hospital in Faisalabad, Pakistan. The purpose of this study is to update all the health care members about the ongoing resistance pattern among the common infections like UTI, prevailing in the society.

MATERIAL AND METHODS

This was a Retrospective cross sectional study comprising 187 patients. All patients of either gender of age >15 years till 90 years having a positive urine culture and sensitivity for E.coli were included. A positive urine culture was defined as bacterial growth $\geq 10^4$ CFUs/ml.

MDR E.coli cases were defined as those cases with resistance to two out of three antibiotic classes namely: (1) ßeta-lactamase inhibitors (2) Fluoroquinolones (3) Aminoglycosides. Age, gender, urine WBC's, and results of urine culture and sensitivity were noted on a designed proforma. Main outcome variable was the frequency of MDR E.coli cases among the culture positive E. coli UTI patients.

All the variables were analyzed using SPSS 16. Nominal data were expressed as frequency and percentage while numerical data were analyzed and mean with standard deviation was calculated. To control the effect modifiers, data was stratified for age and gender and post-stratification chi square was applied to see the effect on the outcome. P-value of < 0.05 was taken significant.

RESULTS

In this retrospective study, 187 cases of UTI with a positive culture showing E. coli were identified. Almost two third of these patients were females; 38% patients were male and 62% patients were females, with female to male ratio of about 2:1. Mean age was 51.48 years with a standard deviation of + 17.44, ranging from 18 to 90 years.

Among all the cases of E. coli UTI, frequency of MDR was 66.8% (n=125) and rest 33.2% (n= 62) cases were not MDR UTI. (Table-I). Among these MDR E.coli UTI cases, 63.2% (n=79) were female and rest 36.8% (n=46) were males patients.

MDRE UTI	Cases	Percent
Yes	125/187	66.8%
No	62/187	33.2%

Table-I. Showing the percentage of MDR E.coli cases among the E. coli UTI cases

Among the total 187 cases, 97.3% patients were resistant to beta-lactam antibiotics, 95.7% were resistant to quinolones and 68.4% were resistant to aminoglycosides.

Effect modifiers like age and gender, were controlled through stratification and post stratification chi square test was applied. (Tables-II and Table-III)

Age of the patients was stratified into young, middle, old. Those of 18 to 35 years were grouped into young category, 36 to 60 into middle age and 61 to 90 into old age group.

Post stratification chi square test was statistically significant for all categories of age but not statistically significant for gender.

		MDR E.coli UTIs		Total
		Yes	No	Yes
Age	Young	22	17	39
	Middle	68	29	97
	Old	35	16	51
Total		125	62	187

Table-II. Post- stratification chi square applied for age in relation with MDR E.coli UTI cases Chi square test = 2.45 p-value = 0.293

		MDR E.coli UTIs		Total
		Yes	No	Yes
Gender	Male	46	25	71
	Female	79	37	116
Total		125	62	187

Table-III. Post- stratification chi square applied for gender in relation with MDR E.coli UTI cases Chi square test = 0.218 p-value = 0.640

When comparing frequencies of the MDR E.coli UTI cases resistant to individual groups of antibiotics, the relation was statistically significant for all the three groups individually i.e. beta-lactams, quinolones and aminoglycosides (with p value < 0.05). (Table-IV,V and VI)

Among the MDR E.coli UTI cases, 99% of the cases were resistant to one or more antimicrobials of the aminoglycoside family (which was statistically significant, p = 0.000). Similarly, 100% cases were resistant to one or more antimicrobials of both the beta-lactams and quinolones group (which was also statistically significant, p = 0.001 and 0.000, respectively).

		MDR E.coli UTIs		Total
		Yes	No	Yes
Resistant to Aminoglycosides	Yes	124	4	128
	No	1	58	59
Total		125	62	187

Table-IV. Showing relation of MDR E.coli UTI cases with cases resistant to Aminoglycosides Chi square test = 165.08 p-value = 0.000

		MDRE UTIs		Total
		Yes	No	Yes
Resistant to Beta-lactams	Yes	125	57	182
	No	0	5	5
Total		125	62	187

Table-V. Showing relation of MDR E.coli UTI cases with cases resistant to beta-lactams Chi square test = 10.358 p-value = 0.001

		MDRE UTIs		Total
		Yes	No	Yes
Resistant to Quinolones	Yes	125	54	179
	No	0	8	8
Total		125	62	187

Table-VI. Showing relation of MDR E.coli UTI cases with cases resistant to quinolones Chi square test = 16.850 p-value = 0.000

DISCUSSION

Urinary tract infections (UTIs) are a major burden to the health care as it is estimated that around 150 million UTIs occur yearly worldwide.[1] Enterobacteriaceae, gram negative rod, being the most common agent behind all UTIs, is also becoming prevalent in Pakistan and with the development of multiple antimicrobial resistance. Choice of antimicrobial for treatment depends on the susceptibility profiles of the Enterobacteriaceae.[4]

The European Antimicrobial Resistance Surveillance Network (EARS-Net) have reported that antimicrobial resistance developed by E. coli and K. pneumonia is so much that antibiotics used as first line agents are no more effective in treating common UTIs. A survey done in 2014 in Italy reported that MDRE were mostly resistant to aminopenicillins (65%), aminoglycosides (19%) and fluoroquinolones (44%). More surveys have shown that those populations with more than 25% antimicrobial resistance are of north Europe.[14]

In a study done by Ukah UV et al a total of 399 women were recruited; 164 women had a UTI caused by E. coli resistant to 1 antimicrobial classes and 98 had a UTI caused by E. coli resistant to 3 antimicrobial classes. After adjustment for age, student health service (region of Canada) and either prior antibiotic use or UTI history, consumption of processed or ground chicken, cooked or raw shellfish, street foods and any organic fruit; as well as, contact with chickens, dogs and pet treats; and travel to Asia, were associated with an increased risk of UTI caused by antimicrobial resistant E. coli. A decreased risk of antimicrobial resistant UTI was associated with consumption of apples, nectarines, peppers, fresh herbs, peanuts and cooked beef.[15]

Awasthi TR, and colleagues reported in their study that among the patients presenting with urinary complaints in the outpatient department about 26% (98/384) patients had positive urine cultures and showed bacterial growth. Similar to our study, patients presenting in his study were one third males and two third females and among them only 19% were diagnosed with culture positive UTI and among females 30% had positive urine cultures. (The difference was found statistically significant ($p<0.05$). E. coli was the causative agent in more than half of the culture positive UTIs (53%), second slot was occupied by K. pneumoniae (22%), followed by Pseudomonas (12%), Proteus (9%) and Staphylococcus (4%). In the treatment of these UTI patients, gentamicin and ceftriaxone was found effective in more than half of the cases nitrofurantoin in 46% cases, Cotrimoxazole (33%), ofloxacin (30%), nalidixic acid (16%), and ampicillin in only 5% cases.[16]

In a meta-analysis, Tenney J, et al reported that 16/20 studies pointed out that the major risk factor leading to MDR microbes in urinary tract is antibiotic abuse and age; other factors includes urinary catheterization, and history of hospital stay and UTI.[17] McAllister R, et al studied UTI cases reported in the residents of nursing homes. UTI was a very common presentation; mostly having pyuria (14.8% cases of old age).[18]

Castillo FR, et al reported that about 63 percent of the strains causing E. coli UTI were MDR and was more common among the females (78%). Among these 78% cases, 40% were female children of less than 10 years and most were resistant to trimethoprim–sulfamethoxazole, ampicillin, and ampicillin–sulbactam. Most of the male cases were fluoroquinolone-resistant and MDR-phenotype.[19]

Unlike our study, Linsenmeyer K, et al in his study identified more than 100 cases of MDR UTIs mostly due to Gram-negative microbes, with about 90% of males and average age was 72.8 years and >90% cases were males.[20]

Ukah UV, et al reported that in during the study period of about 2 and a half years in their setting, among the positive urine cultures done, 73.8% were positive for E. coli, with about 60% female cases, similar to our study. Among these female patients, about 24% were caused by E. coli with 24.6% MDRE UTI cases.[21]

Mutters NT, et al reported that among the E. coli UTI cases 54.5% (121/222) were MDRE cases[22] which was lesser than that in our study. Woodford HJ, et al[23] reported that among the diagnosed UTI patients admitted in the emergency department about 40% were not having any painful urination or frequent urination and most of these were of old age, causes behind were genital or urinary abnormalities, renal stones dehydration, and diabetes. Presenting complaints were not noted in our study as it was a retrospective study, we had limited data available.

Elsayed TI, et al reported after a detailed study that the resistance pattern of the MDRE UTI for various group of antibiotics showed that almost all were resistant to ampicillin and two third of these from Nalidixic acid; 95% of the isolates were found to be multidrug resistant.[24]

Khawcharoenporn T, et al reported that in his study 62/492 diagnosed UTI patients were having non-Enterobacteriaceae UTIs and rest, 87 percent of the total patients, were having Enterobacteriaceae UTI. Median age was 44 years with a range of 14–101 years with most of the cases of female gender (80%). About 14% of these cases were having obstruction in the urinary tract like renal stone, ureteric stone, CA urinary bladder, CA vagina, or BPH. More than half of these were having lower urinary tract infection 19% were MDRE UTI and 81% were not multidrug resistant E. coli UTI.[25]

Conica E, et al concluded that fosfomycin could be taken as first-line agent against simple and recurrent UTIs, as it is safe and have targeted activity. Many studies have supported this, but more clinical trials should be done.[26] Our region is endemic of MDRE UTI cases but still nitrofurantoin and fosfomycin are seen to be very effective in more than ninety percent of countries.[27]

MDR E.coli cases are increasing day by day in our country because of the fact that physicians are switching patients from intravenous antibiotics to oral antibiotics without completing the dosage and duration of one antibiotic just to facilitate the patients or some patients themselves stop the antibiotic when they are symptom free.

After all the discussion, it is clear that the choice of antibiotic in the management of MDR E.coli cases should be based on susceptibility testing and it could be the best strategy in combating these infections.

For the generation of proper guidelines for the management of MDR E.coli UTI cases its prevalence should be estimated among the population along with their susceptibility patterns; this still needs a lot of research in our country. World is moving toward rapid diagnostic tools to identify these microbes, thus guiding in the most suitable immediate treatment.[28]

CONCLUSION

With the rise in the microbe's resistance to multiple drugs, new therapeutic strategies are to be designed after analyzing our population's susceptibility pattern. It is not less than a challenge for physicians of a developing nation like Pakistan to treat MDR E.coli UTI cases while taking care of the cost of treatment and controlling the disease burden at the same time.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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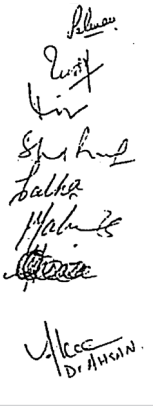
1	Salman Azhar	Data collection, data analysis, paper writing.	
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