ORIGINAL ARTICLE

Susceptibility patterns of common uropathogens to oral antibiotics in adults and their role in empiric treatment of urinary tract infection

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Abstract:

Objective: To determine the frequencies of ESBL and Carbapenemase producing uropathogens and their susceptibilities to oral antibiotics in adults in a tertiary care hospital in Peshawar.

Material and Methods: This retrospective study was conducted at Surgical-B Unit of KTH, Peshawar from January 2016 to December 2017. Adult patients whose urinalysis showed numerous pus cells on microscopy were included. Antimicrobial profiling was done by Kirby Bauer Disc Diffusion method. ESBL detection and screening for Carbapenem resistant strains was done by routine phenotypic methods. Frequencies and percentages of common uropathogens in the adult age group were calculated and their susceptibility patterns to different oral antibiotics was determined. SPSS 23 was used for data analysis.

Results: Of the 2,100 urine samples processed, 762 (36.3%) showed significant growth, of which 407 (53.4%) were multidrug resistant. E.coli was isolated in76.9% cases. ESBL producers comprised 49.3% and carbapenemase producers 4.2% of the total growths. Uropathogens showed high sensitivity to Fosfomycin (91.3%) and increased resistance towards Fluoroquinolones (77-80%), Cefixime (89.2%), Trimethoprim-Sulphamethoxazole (89.5%) and Ampicillin (94.4%).

Conclusion: Fosfomycin has increased sensitivity for ESBL and carbapenem resistant strains of E.coli. Therefore, the rising antimicrobial resistance against Fosfomycin mandates it's cautious use in empirical treatment of UTI.

Keywords: Urinary tract infection, antimicrobial susceptibility, ESBL, Carbapenem-Resistant uropathogens, Empiric treatment

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Introduction:

To this day, urinary tract infection (UTI) remains the most prevalent infectious disease around the globe with a figure of 150 million people being affected worldwide.[1] In the United States, the economy faces a 3.5 billion dollar burden each year due to the morbidity caused by these infections.[2] UTI is the most common nosocomial infection, accounting for 40% of all hospital-acquired infections,[3] 70–80% of which are caused by an indwelling urinary catheter.[4]

The various gram negative uropathogens are now resistant to the first line drugs of choice for UTI. Of these, the Extended-spectrum β-lactamase (ESBL) and carbapenemase-producing enterobacteriaceae and multi-drug resistant (MDR) Pseudomonas aeruginosa are of significant concern.[5] In 2013, the U.S. Centers for Disease Control and Prevention (CDC) issued warnings about the scarcity of new treatments to combat these infections and laid emphasis on the ability of these organisms to develop drug resistance.[6] In a meta-analysis conducted by Costelloe et al, a major cause of this rising antimicrobial resistance was found to be inappropriate use of antibiotics at the primary level.[7]

The shifting trends in antimicrobial susceptibilities has made empiric therapy a challenge for

Table 1: *Table-I: Frequency of Uropathogens and their percentage (%) distribution among different gender, age and admission groups & % ESBL, % MDR.* MDR is defined as resistance to three or more than three drug classes

			%Gender (n)		% Age (n)			% Mode of admission (n)		% Frequency of ESBL, Carbapenem resistant and MDR strains (n)		
S.No	Organisms Isolated	% (n) isolates	males	females	Young adults	Middle aged adults	Old age adults	In-patients	Out- patients	ESBL strains	Carbapenemase resistant strains	MDR (%)
1	Escherichia coli	76.9 (586)	29 (170)	71 (416)	25.9 (152)	33.8 (198)	40.3 (236)	38.4 (225)	61.6 (361)	58 (340)	4.3 (25)	52.6 (308)
2	Citrobacter	7.1 (54)	35.2 (19)	64.8 (35)	27.8 (15)	24.1 (13)	48.1 (26)	31.5 (17)	68.5 (37)	37 (20)	0.1 (3)	35.2 (19)
3	Morganella	4.9 (37)	35.1 (13)	64.9 (24)	32.4 (12)	43.2 (16)	24.3 (9)	27 (10)	72.9 (27)	37.8 (14)	0.1 (2)	40.5 (15)
4	Enterobacter	4.6 (35)	28.6 (10)	71.4 (25)	45.7 (16)	25.7 (9)	28.6 (10)	34.3 (12)	65.7 (23)	48.6 (17)	0.03 (1)	60 (21)
5	S. aureus	3.5 (27)	18.5 (5)	81.5 (22)	55.5 (15)	29.6 (8)	14.8 (4)	44.4 (12)	55.6 (15)	0	0	29.6 (8)
6	Pseudomonas	2.5 (19)	15.8 (3)	84.2 (16)	15.9 (3)	21.1 (4)	63.2 (12)	73.7 (14)	26.3 (5)	42.1 (8)	0	63.2 (12)
7	Klebsiella	0.4 (3)	33.3 (1)	66.7 (2)	-		100 (3)	66.7 (2)	33.3 (1)	-	-	-
8	Proteus	0.1 (1)	-	100 (1)	-	-	100 (1)	0	100 (1)	-	-	-

P Value<0.05 is taken as statistically significant

Table 2: *Susceptibilities (resistance pattern) of uropathogens to oral antibiotics:*

		% resistance (n)													
S. No	Organisms Isolated	Total Organisms (n)	Fosfomycin	Doxycyclin	Amoxicillin-Clavulanate	Moxifloxacin	Ciprofloxacin	Ofloxacin	Sparfloxacin	Norfloxacin	Enoxacin	Monobactams	Cefixime	Trimethoprim-Sulphamethoxazole	Ampicillin
1	Escherichia coli	586	7 (45)	45.2 (265)	67.9 (398)	81.2 (476)	81.1 (475)	81.6 (478)	87.6 (513)	89.4 (524)	84.6 (496)	88.9 (521)	90.4 (530)	89.2 (523)	94.3 (553)
2	Citrobacter	54	11(6)	38.8 (21)	59.3 (32)	68.5 (37)	70.4 (38)	70.4 (38)	74.1 (40)	72.2 (39)	72.3 (39)	70.4 (38)	88.9 (48)	98.1 (53)	98.1 (53)
3	Morganella	37	10 (4)	43.2 (16)	45.9 (17)	68.5 (17)	43.2 (16)	45.9 (17)	43.2 (16)	45.9 (17)	48.6 (18)	62.2 (23)	78.4 (29)	89.2 (33)	91.9 (34)
4	Enterobacter	35	8.5 (3)	51.4 (18)	52.8 (29)	74.3 (26)	74.3 (26)	74.3 (26)	74.3 (26)	74.3 (26)	74.3 (26)	84.6 (31)	94.3 (33)	91.4 (32)	97.1 (34)
5	S. aureus	27	15 (4)	29.6 (8)	48.1 (13)	66.6 (18)	70.4 (19)	70.4 (19)	70.4 (19)	70.4 (19)	70.3 (19)	81.5 (22)	74.1 (20)	77.8 (21)	88.9 (24)
6	Pseudomonas	19	5.5 (1)	26.3 (5)	68.9 (15)	78.9 (15)	73.7 (14)	78.9 (15)	84.2 (16)	82.5 (17)	83.2 (16)	78.9 (15)	84.2 (16)	84.2 (16)	89.5(17)
7	Klebsiella	3	-	33.3 (1)	-	33.3 (1)	33.3 (1)	33.3 (1)	33.3 (1)	33.3(1)	33.3 (1)	66.6 (2)	100 (3)	100(3)	100 (3)
8	Proteus	1	-	-	-	-	-		-	-	-	-	-	-	-
	P values:		0.09	0.39	0.05	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	0.004	0.05	0.22	0.66

Statistical test used: Chi square analysis. Significant at p-value of < 0.05 n: number of uropathogens

today's clinicians.[8]The condition in Pakistan is even worse due to the limited data availability, both locally and nationally and a crucial lack of evidence-based research to guide in selection of empiric antibiotics.[9] Prescription of antibiotics without drug susceptibility testing is common practice, which is increasing the frequency of resistant bacterial strains and adding to the economic burden.[10] The aim of our study is to determine local prevalence of common uropathogens and to determine the ESBL and Carbapenem resistance in UTI patients and oral antibiotic susceptibilities to these strains in order to provide new surveillance data that may serve as a useful guide in empiric therapy of UTI for tertiary care-level clinicians of Pakistan.

Material and Methods:

After obtaining approval from the Institutional Review Board of Khyber Teaching Hospital, Pe-

shawar, this retrospective study was conducted at Surgical B-Unit of Khyber Teaching Hospital, Peshawar for a period of two years, from January 2016 to December 2017. Using non probability consecutive sampling technique under WHO software for sample size calculation, a total of 2100 patients belonging to both genders, between the ages of 16 to 90 years, presenting to the outpatient and inpatient department with symptoms of UTI and numerous pus cells on urinalysis were included. Under aseptic techniques, midstream urine specimens were collected from each patient and subjected to routine biochemical tests. Uropathogens were identified via gram staining and grown on MacConkey agar and blood agar plates incubated aerobically for 24 hours at 37°C. Susceptibility testing was done by Kirby-Bauer Disc diffusion method and minimum inhibitory concentration (MIC) method on Mueller-Hinton agar and interpreted in accordance with Clinical Laboratory Standard Institute Guidelines (CLSI) 2014.[11] Isolates were tested for ESBL producing strains by Double Disc Diffusion Technique and for Carbapenemase producing strains by routine phenotypic methods. Multidrug resistant organisms were defined as those resistant to three or more than three classes of antibiotics tested. Culture reports showing mixed growth or no growth were excluded from the study as were patients who were on antibiotics for 48-hours prior to specimen collection. All urine cultures were performed and reported by microbiology department of Khyber Teaching Hospital, Peshawar. In our study only those antibiotics were included that were tested for all of the urine specimens. SPSS 23 was used for data analysis. Chi square test was used to compare between different variables and $p<0.05$ was considered statistically significant.

Results:

Of the 2100 urine samples processed, 762 (36.28%) showed significant growth of pathogens. The age range of patients was between 16-90 years, average being 48.5±18.5 SD. More organisms were isolated from females (71%) than from males (29%). More cases of UTI were recorded among old age adults (55-90 years, 39.5%) than young (16-35 years, 28%) and middle-aged adults (36-55 years, 32.5%). Hospitalized patients made up 292(38.3%) cases whereas 470(61.7%) cases were seen as out-patients (OPD). The majority of isolates comprised of gram negative aerobic rods (96.5%) while gram positive cocci accounted for the remaining 3.5%. The frequencies of common uropathogens isolated are given in Table-I. E.coli (76.9%) was the most common organism isolated.

Table-I shows the age and gender-wise data regarding the prevalence of uropathogens. . Results show that E.coli (61.6%) was more common in OPD patients, where as Pseudomonas (73.7%) and Klebsiella (66.7%) were more common in hospitalized patients ($p=0.031$). Of the 762 isolates, 407(53.4%) were multidrug resistant with same distribution among males and females of all ages ($p>0.05$). Prevalence of MDR uropathogens was high among hospitalized patients ($p<0.01$). E.coli (52.6%), Enterobacter (60%), and Pseudomonas (63.2%) were more multidrug resistant than other organisms ($p=0.025$).

ESBL resistant strains comprised 49.3% and carbapenem resistant strains 4.2% of the positive growths. E.coli (58%) and Enterobacter (48.6%) were the most prevalent ESBL producers whereas E.coli alone accounted for the majority of carbapenem resistant strains (84%). A major chunk of ESBL and carbapen resistant strains (51.1% and 98% respectively) were isolated from hospitalized patients ($p<0.01$) irrespective of age and gender and all of them were MDR (100%). Frequencies are listed in Table-I.

Of the 762 cases, 93.9% were susceptible to all the tested oral antibiotics whereas 6.14% showed sensitivity only to injectable antibiotics in the order of: Imipenem (94.4%), Meropenem (93.7%) Amikacin (92.6%) Piperacillin-tazobactum (91.2%) Cefoperazone-sulbactam (90.3%) and Gentamicin (89.6%). Among the oral antibiotics, uropathogens showed the highest sensitivity to Fosfomycin (91.3%) and Doxycycline (56.2%). Among the Fluoroquinolones

Table 3: *Resistance Pattern (%) of UropathogensAmong Inpatients & Outpatients*

S. No	Organisms Isolated	% Total isolates (n)	In-patients			Out- patients		
			% isolates (n)	% Sensitivity to Fosfomycin (n)	% Resistance to Fosfomycin (n)	% isolates(n)	Resistance to Fosfomycin	Sensitivity to Fosfomycin
1	Escherichia coli	76.9 (586)	38.4 (225)	89.3 (201)	10.7(24)	61.6 (361)	5.8(21)	94.2(340)
2	Citrobacter	7.1 (54)	31.5 (17)	76.5 (13)	23.5(4)	68.5 (37)	5.4(2)	94.6(35)
3	Morganella	4.9 (37)	27 (10)	80 (8)	20(2)	72.9 (27)	7.4(2)	92.6(25)
4	Enterobacter	4.6 (35)	34.3 (12)	91.7(11)	8.3(1)	65.7 (23)	8.7(2)	91.3(21)
5	S. aureus	3.5 (27)	44.4 (12)	66.7(8)	33.3(4)	55.6 (15)	20(3)	80(12)
6	Pseudomonas	2.5 (19)	73.7 (14)	92.8(13)	7.1(1)	26.3 (5)	0	100(5)
7	Klebsiella	0.4 (3)	66.7 (2)	100(2)	0	33.3 (1)	0	100(1)
8	Proteus	0.1 (1)	0	0	0	100 (1)	0	100(1)
	P values		P<0.01			P<0.01		

(FQs), uropathogens showed increased pattern of resistance; Moxifloxacin (77.6%), Ciprofloxacin (77.4%), Ofloxacin (78.1%), Sparfloxacin (79.1%) Norfloxacin (79.1%) and Enoxacin (80.1%).

Table-II shows the pattern of resistance (in percentage) to the various antibiotics .

The antibiotics tested showed similar sensitivity and resistance patterns among males and females of all age groups. OPD patients were more sensitive to Fosfomycin and Doxycycline as compared to hospitalized patients ($p<0.01$), however they were highly resistant to all the other antibiotics.

Table-III shows the pattern of resistance (percentage) among OPD and hospitalized patients for the various oral antibiotics tested. All uropathogens showed similar antibiotic susceptibility patterns except for E.coli which exhibited more resistance towards fluoroquinolones and monobactams ($p<0.01$).

Susceptibility of Fosfomycin for ESBL resistant strains was sensitive (91.8%) and resistance (9.2%) and for carbapenem resistant strains: sensitivity (95.1%) and resistance (4.9%). Both ESBL and carbapenem resistant strains showed significant resistance towards the other oral antibiotics. For ESBL resistant strains, all the intravenous (IV) antibiotics showed 90-98% sensitivity however for carbapenresistant strains the susceptibilities were varied: Amikacin (94%), Gentamicin (93.1%), Piperacillin-tazobactum (87.6%) and Cefoperazone-sulbactam (75.4%).

Discussion:

UTI is the most frequently diagnosed infectious disease affecting individuals both in the hospital and the community and is more common in females than in males.[12] Amongst the uropathogens, E.coli is known to be the leading cause of UTI in adults. It is one of the nine bacteria of international concern according to WHO's report on antimicrobial resistance.[13] Likewise, in our study females(71%) were mostly infected, predominantly by E.coli (76.9%). In our study Pseudomonas and Klebsiella were found to be the major cause of hospital acquired UTIs and E.coli the main cause of community acquired UTI which is in accordance with the recent global epidemiological data.[14] A study from Peshawar reported a figure of 58.9% E.coli as MDR[15] whereas in our study 53.4% of the isolates were multidrug resistant, possibly due to the fact that most of our population comprised of outpatients.

Multidrug resistance in gram negative organisms

is partly attributed to their ability to produce enzymes such as ESBLs and carbapenemases. In Asian-pacific countries, 60-80% ESBL producers are harbored in hospitals. The prevalence of ESBL producing enterobacteriaceae in Pakistan is reported to be 40% and in KPK figures are above 30%.[16] Our figures show a 49.3% prevalence of ESBL producers comparable to a study done by Jabeen K. et al (40%)[17] but less as compared to Ullah F. et al (56.89%).[18]

A major pubic health threat is the rapid emergence of carbapenem resistant enterobacteriaceae (CRE) which render carbapenems ineffective. Carbapenems are the last line drugs for the management of critically ill patients. Reports from the AKU Hospital showed that carbapenem resistance had risen for clinical isolates of E. coli and K. pneumoniae, from 1% and 3% respectively, in 2009 to 5% and 18%, respectively, by 2014.[19] Our reported prevalence for carbapenem resistant E.coli was 4.2%.

In developing countries (like Pakistan), the resistance of E.coli to FQs especially Ciprofloxacin is increasing[20] which is consistent with the findings of our study. Previously, international guidelines recommended trimethoprim-sulfamethoxazole, ciprofloxacin and ampicillin as first line empiric prescriptions for UTI.[21] Unfortunately, these are still being prescribed in our setup, resulting in countless treatment failures, owing to the high resistance to these antibiotics as shown in our study. As a result, health care facilities are over burdened by patients presenting with recurrent and multidrug resistant infections. For effective treatment, surveillance studies should be done regularly to keep clinicians up to date with the local data of each area.[22]

Our analysis showed that Fosfomycin was the most sensitive drug in both hospital and community acquired UTIs, irrespective of age and gender. Furthermore, it was sensitive to almost 91.8% ESBL producers and 95.1% carbapenemase producers, the figures being consistent with international data.[23] However, the resistance exhibited by Fosfomycin for both strains: 9.2% and 4.9% respectively is contrary to the 100% susceptibility seen in western countries.[21] These results show that antimicrobial resistance against Fosfomycin is on the rise. In the United States and Canada, Fosfomycin is being used as a first-line drug for acute uncomplicated UTIs[21] and recently, the same has been adopted by our clinicians. Our statistics and local surveillance data, though limited, suggest that we prescribe Fosfomycin with caution and after proper susceptibility testing in order to avoid resistance. Being one of the few antibiotics to treat CRE infections,[23] Fosfomycin must be reserved till last while prescribing drugs for empiric therapy. If the current trends of over the counter prescription of antibiotics persist, resistance to Fosfomycin will increase so much that clinicians will have no choice but to use carbapenemsas first line drugs for simple uncomplicated UTIs[24] presenting in OPDs. This would mean no availability of oral therapy for UTI and consequently increased hospitalizations.

According to our results, more than 90% of both hospital and community acquired UTIs can be managed with oral antibiotics like Doxycyclin and Amoxicillin in suitable settings, thereby unnecessary hospital admissions can be avoided. Furthermore, hospitalized patients can be offered oral therapy which may be curative and cost effective at the same time. According to a recent Cochrane review, it was found that oral antibiotics were as effective as intravenous antibiotics in treating UTI.[25]

Our study had certain limitations. Complicated and uncomplicated UTI cases were not identified. So prevalence of resistant strains in those groups could not be ascertained. Furthermore susceptibility to Nitrofurantoin was not checked in all cases so the exact resistance to the drug could not be determined. Also, now-a-days PCR and gene detection methods remain superior for the detection of ESBL strains.[16] Unfortunately due to the lack of such laboratory facilities, we could not rule out false-negatives from our estimated prevalence.

Conclusion:

The rising antimicrobial resistance towards

Fosfomycin in Pakistan by ESBL and carbapenemase producing E.coli is a concerning issue which has to be addressed. Fosfomycin may be the only oral drug left against ESBL & CRE infections, so it must be reserved for culture positive cases only and must not be routinely prescribed. Regular surveillance studies are required for knowing the exact microbial profile and patterns of resistance of a given area to guide in empirical prescriptions.

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Role and contribution of authors:

Dr Hizbullah Jan, conception and design, Helped in final approval.

Dr Misbah Riaz, analysis & interpretation of data, drafting of article.

Dr Tufail Ahmad, conception & design and Acquisition of data

Dr Mah Muneer Khan, Final revision and critical evaluation of intellectual content.

Dr Erum Khalid, helped in collection of references and also helped in discussion writing.

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