Original Article

Urinary tract pathogens and their patterns of resistance to commonly used antibiotics

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Objective: To evaluate the prevalence of certain microorganisms in urine and their antibiotic sensitivities.

Methodology: This retrospective descriptive study was done collecting data from records of Chughtai Lab between May 2016 and March 2018 from their branch near Mayo Hospital, Lahore. By convenience sampling, only those 290 out of total 722 reports of urine culture and sensitivity were included, which yielded at least one microorganism. All age groups and genders were included. All negative reports were excluded.

Results: Mean age of patients was 59.49years (range 1-90). A total of 290 reports yielded 319 microorganisms among which 29 reports showed two organisms each. *Candida spp.* co-existed in 26 cases. *E.coli* was found to be the most prevalent organism; 181/319 (56.74%), followed by *Enterococcus faecalis*; 58/319 (18.18%). Most active antibiotics against gram positive organisms were; Linezolid (100%, n=58), Doxycycline (96.55%, n=58), Vancomycin (91.22%, n=57) and Nitrofurantoin (70.68%). Most efficient antibiotics against gram negative organisms were; Fosfomycin (90.91%, n=198), Carbapenems i.e. Imipenem and Meropenem (89.19%, n=259), Amikacin (85.6%, n=250), Cefoperazone plus Sulbactam (81.62%, n=234), Piperacillin plus Tazobactam (80.54%, n=257) and Nitrofurantoin (72.88%).

Conclusion: *E.coli* was the most prevalent organism and Fosfomycin and Carbapenems were most effective antibiotics. Fluoroquinolones didn't appear to be a good choice for treatment of UTIs. (Rawal Med J 202;45:22-26).

Keywords: Antibiotics, Antimicrobial Drug Resistance, Bacteriuria, Cystitis, Gram Negative Bacteria, Gram Positive Bacteria, Urinary Tract Infections.

INTRODUCTION

Urinary tract infections (UTIs) are among the most prevalent bacterial infections of humans. They include urethritis, cystitis, pyelonephritis and urosepsis.[1] Women are more likely to acquire UTIs than men.[2] About half of the women will experience an episode of UTI in their lifetime.[3] This can be explained by the shorter length of female urethra and shorter distance between anus and external urethral opening. Other risk factors for UTIs include old age, catheterization, pregnancy, spinal cord injury (causing neuropathic bladder), urological abnormalities, diabetes mellitus and multiple sclerosis.

Urological abnormalities that predispose to UTIs are the ones that cause obstruction and stasis, including stone disease, benign prostatic hyperplasia, pelvi-ureteric junction obstruction and neuropathic bladder.[4] Gram negative organisms especially from *Enterobacteriaceae* family are more prevalent as compared to Gram positive organisms. *E. coli* was found to be the most prevalent organism in most of the studies while other common organisms include *Klebsiella pneumonae*, *Proteus mirabilis, Staphylococcus aureus, Staphylococcus saprophyticus* and *Pseudomonas aeruginosa.*[2,4,5]

Antibiotic resistance is an emerging problem and WHO has declared it as a major threat to public health.[6] Susceptibility of most organisms to most commonly used antibiotics is very low. But most of the organisms are found to be sensitive to imipenem, piperacillin+tazobactam, cefoperazone+sulbactam, amikacin and nitrofurantoin.[2,5,7,8] Empirical antibiotic therapy is based on previous knowledge of prevalence of certain organisms and their antibiotic susceptibilities. A study by Biswas et al revealed that fluoroquinolones were not a favorable choice for cystitis while nitrofurantoin was found to be a better option.[9] Antibiotic resistance is a constantly changing and evolving domain.[10] The

aim of this study was to evaluate the prevalence of certain microorganisms in urine and their antibiotic sensitivities so that better choices can be made regarding empirical antibiotic therapy.

METHODOLOGY

It was a retrospective descriptive study done by analyzing data from records of Chughtai Lab branch located near Mayo Hospital, Lahore that caters a tertiary care hospital as well as general public hospital. A total of 722 reports of urine culture and sensitivity were obtained from records of duration May 2016 to March 2018. Out of these, only those reports were included in the study which yielded at least one microorganism and had bacterial count of above $10^{\wedge 5}$ CFU. Culture reports other than urine, those with bacterial count below $10^{\wedge 5}$ CFU and those yielding no microorganism were excluded from the study.

The information acquired included patient's demographic data (i.e. age & gender) along with the organism isolated from culture and its antimicrobial sensitivity pattern as tested according to CLSI 2016 guidelines.[11]

Statistical analysis: Data were analyzed in SPSS version 20. Demographic parameters of patients were assessed by descriptive statistics using mean and standard deviation. The frequencies of microorganisms and sensitivity patterns of microorganisms against different antibiotics were tabulated.

RESULTS

Out of 722 reports, 290 reports were included in the study which yielded 319 organisms. Among those, 119 (41%) reports were from males while 171 (59%) were from females. Reports form all age groups were present (1-90 years) and peaked at around 60-70 years of age (mean 59.49 years).

From the total 319 organisms, 59 were gram positive whereas 260 were gram negative. Among 290 culture reports, 29 showed growth of two organisms. *E.coli* was found to be the most prevalent organism (56.74%) followed by *Enterococcus faecalis* (18.18%) (Figure). In 26 cases, *Candida spp.* co-existed with the bacteria, 18 of which were in female patients while 8 belonged to the male patients. Mean age for these patients were 59±18.7.

Figure. Microorganisms isolated

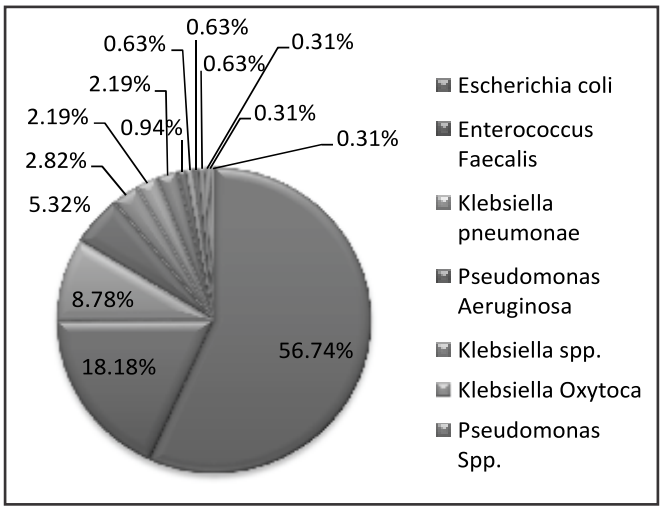

Table 1. Antibiotic activity against gram positive and negative organisms.

Drugs	Gram Positive	Gram Negative
	Sensitive/ Resistance	Sensitive/ Resistance
Linezolid	58/0 (100%)	1/0 (100%)
Vancomycin	52/5 (91.22%)	1/1 (50.00%)
Fosfomycin	*Not tested*	180/18 (90.90%)
Imipenem	1/1 (50.00%)	231/28 (89.18%)
Meropenem	1/1 (50.00%)	231/28 (89.18%)
Amikacin	4/0 (100%)	214/36 (85.6%)
Piperacillin plus Tazobactam	*Not tested*	207/50 (80.54%)
Cefoperazone plus sulbactam		191/43 (81.62%)
Nitrofurantoin	41/17 (70.07%)	172/64 (72.88%)
Ticarcillin plus clavulanic acid	*Not tested*	8/14 (35.35%)
Ampicillin	33/26 (55.93%)	0/1 (0.00%)
Amoxicillin	33/26 (55.93%)	0/1 (0.00%)
Amoxicillin plus clavulanic acid	34/25 (57.62%)	33/202 (14.04%)
Ampicillin plus sulbactam	34/25 (57.62%)	33/202 (14.04%)
Cefipime	1/1 (50.00%)	82/176 (31.78%)
Cefoperazone	1/1 (50.00%)	47/187 (20.08%)
Cefotaxime	1/1 (50.00%)	47/187 (20.08%)
Cefuroxime	1/1 (50.00%)	35/196 (15.15%)
Ceftazidime	1/1 (50.00%)	57/202 (22.01%)
Ceftriaxone	1/1 (50.00%)	48/187 (20.42%)
Cephalexin	1/1 (50.00%)	1/167 (0.59%)
Cephradine	1/1 (50.00%)	1/166 (0.59%)
Cefaclor	1/1 (50.00%)	35/196 (15.15%)
Cefixime	1/1 (50.00%)	48/187 (20.42%)
Aztreonam	*Not tested*	26/70 (27.08%)
Gentamicin	6/24 (20.00%)	115/139 (45.27%)
Tobramycin	3/1 (75.00%)	95/161 (37.10%)
Doxycycline	56/2 (96.55%)	92/131 (41.25%)
Nalidixic acid	*Not tested*	21/210 (9.09%)
Ciprofloxacin	13/46 (22.03%)	52/208 (20.00%)
Levofloxacin	13/46 (22.03%)	52/208 (20.00%)
Norfloxacin	13/46 (22.03%)	52/207 (20.07%)
Moxifloxacin	1/0 (100%)	41/194 (17.44%)
Trimethoprim plus sulphamethoxazole	2/0 (100%)	49/184 (21.03%)
Pipemidic acid	*Not tested*	20/213 (8.58%)
Polymyxin B		19/0 (100%)
Colistin		19/0 (100%)

Table 2. Antibiotic susceptibility of most common microorganism.

Drugs	Escherichia coli	Enterococcus faecalis	Klebsiella pneumonae	Pseudomonas Aeruginosa
	Sensitive/ Resistance	Sensitive/ Resistance	Sensitive/ Resistance	Sensitive/ Resistance
Linezolid	*Not tested*	57/0 (100%)	*Not tested*	*Not tested*
Vancomycin		52/5 (91.23%)		
Fosfomycin	164/14 (92.14%)	*Not tested*	5/0 (100%)	
Imipenem	169/12 (93.37%)		24/4 (85.71%)	13/4 (76.47%)
Meropenem	169/12 (93.37%)		24/4 (85.71%)	13/4 (76.47%)
Amikacin	157/16 (90.75%)	2/0 (100%)	23/5 (82.14%)	12/4 (75.00%)
Piperacillin plus Tazobactam	151/28 (84.36%)	*Not tested*	19/9 (67.86%)	14/3 (82.35%)
Cefoperazone plus Sulbactam	150/30 (83.33%)		21/7 (75.00%)	*Not tested*
Nitrofurantoin	139/42 (76.80%)	39/18 (68.42%)	18/10 (64.28%)	
Amoxicillin plus clavulanic acid	24/157 (13.26%)	33/25 (56.90%)	4/24 (16.67%)	
Ampicillin plus Sulbactam	24/157 (13.26%)	33/25 (56.90%)	4/24 (16.67%)	
Amoxicillin	*Not tested*	33/25 (56.90%)	*Not tested*	
Ampicillin		33/25 (56.90%)		
Cefipime	52/129 (28.73%)	1/1 (50.00%)	8/20 (28.57%)	9/7 (56.25%)
Cefoperazone	34/146 (18.89%)	1/1 (50.00%)	6/22 (21.43%)	*Not tested*
Cefotaxime	34/146 (18.89%)	1/1 (50.00%)	6/22 (21.43%)	
Ceftazidime	35/146 (19.34%)	1/1 (50.00%)	6/22 (21.43%)	6/11 (35.29%)
Ceftriaxone	35/146 (19.34%)	1/1 (50.00%)	6/22 (21.43%)	*Not tested*
Cefixime	35/146 (19.34%)	1/1 (50.00%)	6/22 (21.43%)	
Gentamicin	83/92 (47.43%)	4/25 (13.79%)	13/15 (46.43%)	10/7 (58.82%)
Tobramycin	65/113 (36.52%)	2/0 (100%)	12/16 (42.86%)	10/7 (58.82%)
Doxycycline	67/106 (38.73%)	55/2 (96.49%)	14/12 (53.85%)	Not tested
Ciprofloxacin	30/151 (16.57%)	11/47 (18.96%)	6/22 (21.43%)	10/7 (58.82%)
Levofloxacin	30/151 (16.57%)	11/47 (18.96%)	6/22 (21.43%)	10/7 (58.82%)
Moxifloxacin	30/151 (16.57%)	*Not tested*	6/22 (21.43%)	*Not tested*
Trimethoprim plus sulphamethoxazole	31/148 (17.32%)		9/19 (32.14%)	
Pipemidic Acid	12/167 (06.73%)	*Not tested*	4/24 (14.28%)	
Polymixin B	8/0 (100%)		3/0 (100%)	3/0 (100%)
Colistin	8/0 (100%)		3/0 (100%)	3/0 (100%)

Antibiotics found to be most active against gram positive organisms were; Linezolid (100%, n=58), Doxycycline (96.55%, n=58), Vancomycin (91.22%, n=57) and Nitrofurantoin (70.68%). While against gram negative organisms, most efficient antibiotics were; Fosfomycin (90.91%, n=198), Carbapenems i.e. Imipenem and Meropenem (89.19%, n=259), Amikacin (85.6%, n=250), Cefoperazone plus Sulbactam (81.62%, n=234), Piperacillin plus Tazobactam (80.54%, n=257) and Nitrofurantoin (72.88%) (Table 1). Antibiotic susceptibility of most common microorganisms is shown in Table 2.

DISCUSSION

Male to female ratio in our study was 41:59, which was somewhat different than most other studies which showed a ratio of 30:70.[11] Some studies even show similar ratio as of ours e.g. M:F of 42.3:57.7 by Nerukar et al.[12] But UTIs almost invariably appear to be more prevalent in females.[5,8]

Common organisms causing UTIs were *E. coli, Enterococcus faecalis, Klebsiella pneumonia, Pseudomonas aeruginosa, Klebsiella spp, Klebsiella oxytoca, Pseudomonas spp, Enterobacter cloacae, Acinetobacter baumannii, Staphylococcus aureus, Proteus spp, Proteus mirabilis, Acinetobacter spp* and *Morganella moganii.*[13] These organisms have come in different order of frequency in other studies but *E.coli* was invariably found to be the most prevalent cause of UTI.[14,15] *Enterococcus faecalis* was unique to our study especially because it was a lot more prevalent (18.18%) than most of the others studies.[7,13,16]

Carbapenems (93.37%) were the most effective drug class against *E.coli* followed by amikacin (90.75%), pipercillin plus tazobactam (84.36%) and cefoperazone plus sulbactam (83.33%).[8,14] For *Enterococcus faecalis*, linezolid was 100% effective, followed by doxycycline (96.49%) and vancomycin (91.23%).

Penicillins, cephalosporins and fluoroquinolones did not show inspiring results especially when used without Beta-lactamase inhibitors. Ciprofloxacin was effective only 20% of the time while ceftriaxone and cefixime showed 20.68% and 20.67%, respectively.[17] Low susceptibility rates of fluoroquinolones, trimethoprim plus sulfamethoxazole and third generation cephalosporins can be attributed to their frequent use as they are considered first line agents against UTIs. Moreover, they also have other therapeutic indications warranting their abundant use.[18] A similar study from same hospital by Sabir et al in 2014 showed similar results.[19]

It was observed that whenever *Enterococcus fecalis* was resistant to amino-penicillins (ampicillin, amoxicillin), it was resistant to aminopenicillin + Beta-lactamase inhibitor as well. This implies that resistance of *E. fecalis* to Penicillins is not via beta-lactamases but rather by some other mode. Similar finding was noted with cefoperazone alone versus cefoperazone + Sulbactam against *E. fecalis.* But cefoperazone + sulbactam was significantly superior to cefoperazone alone against all other microorganisms indicating that mode of resistance in these organisms was Beta-lactamase mediated, a finding consistent with study of Shabbir et al.[17]

One limitation we had to face during the study was lack of patient history. Data wasn't available for parameters like duration of symptoms, nature of symptoms, use of any antibiotics prior to sampling for culture, any surgical or pathological abnormality that could contribute to the UTIs or any co-morbidities. But keeping in view the routine practice in our setup, it is safe to assume that many if not all patient had taken at least some antibiotics during the course of illness and that a significant number of cases would be from recurrent UTIs, including nosocomial infections because urine culture and sensitivity is usually not carried out at initial presentation in our setup. Hence the bias of our result to the complicated, recurrent or nosocomial UTIs cannot be ruled out.

CONCLUSION

E.coli was found to be the most prevalent uropathogen. Antibiotics found most effective were Fosfomycin, Carbapenems (Imipenem and Meropenem), Amikacin, Cefoperazone plus Sulbactam and Piperacillin plus Tazobactam while Fluoroquinolones, Co-trimoxazole and third generation Cephalosporins do not seem very effective. For resistant Gram negative organisms

Polymixin B and Colistin are found to be 100% effective

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REFERENCES

1. Bonkat G, Pickard R, Bartoletti R, Bruyère F, Geerlings SE, Wagenlehner F, et al. EAU guidelines on urological infections. Eur Assoc Urol 2017:249:69.
2. Ahmed E. Urinary tract Bacterial pathogens and their sensitivity pattern. J Rawalpindi Med Coll 2014;18:263-4.
3. Foxman B. Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. Disease-a-month. 2003;49:53-70.
4. Paryani JP, Memon SR, Rajpar ZH, Shah SA. Pattern and sensitivity of microorganisms causing urinary tract infection at teaching hospital. JLUMHS 2012;11:97-100.
5. Farooqi BJ, Shareeq F, Rizvi QK, Qureshi HS, Ashfaq MK. Changing pattern of antimicrobial susceptibility of organisms causing community acquired urinary tract infections. J Pak Med Assoc 2000;50:369-73.
6. Mendelson M, Matsoso MP. The World Health Organization global action plan for antimicrobial resistance. South Afr Med J 2015;105:305.
7. Khan IU, Mirza IA, Ikram A, Afzal A, Ali S, Hussain A, Fayyaz M, et al. Antimicrobial susceptibility pattern of bacteria isolated from patients with urinary tract infection. JCPSP 2014;24:840-4.
8. Shabbir M, Ali I, Iman NU. Urinary tract infections and their antibiotic susceptibility patterns in different age and gender groups at a tertiary care hospital of Peshawar, Pakistan. Rawal Med J 2017;42:181-7.
9. Biswas D, Gupta P, Prasad R, Singh V, Arya M, Kumar A. Choice of antibiotic for empirical therapy of acute cystitis in a setting of high antimicrobial resistance. Indian J Med Sci 2006;60:53-8.
10. Smelov V, Naber K, Johansen TEB. Improved Classification of Urinary Tract Infection: Future Considerations. European Urology Supplements 2016 July 1; 15(4): 71-80.
11. Wayne PA. Clinical and laboratory standards institute. Performance standards for antimicrobial susceptibility testing. 26th ed. 2016.
12. Nerurkar A, Solanky P, Naik SS. Bacterial pathogens in urinary tract infection and antibiotic susceptibility pattern. J Pharmaceut Biomed Sci 2012;21:1-3.
13. Jadoon SA, Ahmed A, Irshad R. Spectrum of bacterial culture and drug sensitivity vs resistance in uncomplicated urinary tract infection. J Ayub Med Coll Abbottabad 2018;30:432-8.
14. Ahmad N, Ahmad I, Faqir F, Rehman OU. Antimicrobial susceptibility patterns of uropathogens. J Med Sci 2015;23:105-8.
15. Akram M, Shahid M, Khan AU. Etiology and antibiotic resistance patterns of community-acquired urinary tract infections in JNMC Hospital Aligarh, India. Ann Clinical Microbiol Antimicrobials 2007;6:4.
16. Hameed S, Afzal T, Cheema SM, Momina A, Hussain A. Distribution and susceptibility pattern of urinary tract bacterial pathogens in an outpatient setting. JUMDC 2014;3:26-34.
17. Shabbir M, Iman NU, Shah MZ. Multidrug resistant uropathogens in urinary tract infections and their antibiotic susceptibility patterns. J Med Sci 2018;26:24-7.
18. Hooton TM, Besser R, Foxman B, Fritsche TR, Nicolle LE. Acute uncomplicated cystitis in an era of increasing antibiotic resistance: a proposed approach to empirical therapy. Clinical Infect Dis 2004;39:75-80.
19. Sabir S, Anjum AA, Ijaz T, Ali MA. Isolation and antibiotic susceptibility of E. coli from urinary tract infections in a tertiary care hospital. Pak J Med Sci 2014;30:389-92..