ORIGINAL | INDEPENDENT JOURNAL OF ALLIED HEALTH SCIENCES

IJAHS-0506

ANTIMICROBIAL MULTI DRUG RESISTANCE IN URINARY TRACT INFECTION

Tasneem Ahsan, Endocrinologist MRCP (UK), FRCP (Glasg), FRCP (Edin), FRCP (Lon), FCPS (Pak)
Internist/Endocrinologist Emeritus professor of Medicine, Endocrinology, Ex Dirctor JPMC.
Shumaila Tahir, MBBS (DUHS), FCPS (Medicine) Resident, Resident Physician (Internal Medicine) JPMC,
Medical Officer District East, Department of Health Sindh Government Karachi.
Syeda Anjala Tahir, FCPS (Medicine), MBBS (Dow), Postgraduation JPMC,
Consultant Physician (internal Medicine) Dr. Ruth K.M. Pfau Civil Hospital Karachi.
Haseeb Ahmed Bhatti, MBBS, FCPS (Medicine) resident, Resident Physician, JPMC Karachi.

Date of Received: 22/05/2021 **Date of Acceptance:** 26/05/2021

ABSTRACT

Objective: To determine the frequency of antimicrobial multi-drug resistance in urinary tract infection. **Setting:** Medical unit II of Jinnah post Graduate Medical Center, Karachi. **Study design:** Cross sectional study. **Period:** Six months. 5th September 2016 to 5th March 2017. **Material and Method:** This was a prospective, observational, case series study. Patients with diagnosis of urinary tract infection were enrolled. Detailed history, physical examination and biochemical measurements were recorded. Patients were followed to determine for outcome variable i-e antimicrobial Multi drug resistance. **Results:** Hundred and eight patients fulfilling the inclusion criteria were included in this study. The mean±standard deviation age of study population was 47.92±12.349 years. On analysis of demographics data it was observed. 39(36.1%) were below 40 years of age & 69(63.9%) were of age 40 years and above. 60(55.6%) were males and 48(44.4%) were females.35 (32.4%) patients had DM. 42(38.9%) had Nosocomial infection. 79(73.1%) had duration of disease less than 3days. 64 (59.3%) had hospital stay Less than 5days. On analysis of frequency of outcome variable 29 (26.9%) had MDR. **Conclusion:** Antimicrobial multi-drug resistance is not uncommon in patients with Urinary tract infection. E.coli was frequently cultured organism and was significantly associated with antimicrobial MDR.

Correspondence Address
Shumaila Tahir
Medical Officer
District East, Department of Health Sindh Government Karachi.
shumaila_duhs@yahoo.com

Keywords: UTI, antimicrobial, MDR, culture.

Article Citation: Ahsan T, Tahir S, Tahir A S, Bhatti H. Antimicrobial multi drug resistance in urinary tract infection. **IJAHS,** Jan-Mar 2021;01(10-16):01-07.

INTRODUCTION

Urinary tract infections (UTIs) are among the most common bacterial diseases worldwide. UTI can be asymptomatic or symptomatic, characterized by a wide spectrum of symptoms ranging from mild irritative voiding to bacteremia, sepsis, or even death. One recent study reports that in America UTI increased from12.9 to 18.4 per 10000 people during period 1998 to 2011.[1] In Pakistan the prevalence of UTIs were 11.6%. 8.9% in males and 13.8% in females.[2] Majority of UTIs are not life threatening and do not cause any irreversible damage. However, when the kidneys are involved, there is a risk of irreparable tissue damage with an increased risk of morbidity. Like pyelonephritis, premature delivery and fetal mortality can occur due to UTI in pregnancy. While UTI can cause end stage renal disease in children.[3]

Infection may occur at any part of the genitourinary tract, including urethra, bladder, ureter, renal pelvis, or renal parenchyma. Most infections are caused by retrograde ascent of bacteria from fecal flora to bladder and kidney via urethra, especially in females whom the urethra is shorter and wider. Trauma during sexual intercourse may cause bacterial passage from

urethra upto bladder. Same mechanism may come into play during pregnancy and delivery. Hence anatomical structures of female urethra make them susceptible to UTI.

Bacteria are the major causative organism and are responsible for more than 95% of UTI cases.[4] Escherichia coli is the most frequent infecting organism in acute infections. But other organisms are too commonly involved. It is important to be aware of common pathogens which cause UTI in a particular are. This knowledge along with information regarding possible drug susceptibly/resistance will guide physician to prescribe antibiotic empirically

The pattern of antimicrobial resistance of bacteria producing UTI varies in different regions. There has been a significant increase in resistance of pathogenic strains to ampicillin and cephalosporin noted worldwide. But even more challenging problem is increase in frequency of multi-drug resistance. This problem is much worse in strains of Enter obacteriaceae [multi-drug- resistant Enterobacteriaceae (MDRE).[5] Previously, emerging resistance among the Enterobacteriaceae due to extended-spectrum beta-lactamases (ESBL) had posed a very difficult situation throughout whole world, including in Chicago.[6] Apart from above mentioned mechanism of resistance there have been widespresd reporting of other mechanisms of resistance among urinary pathogens including Klebsiella pneumoniae carbapenemases (KPC) and New Delhi metallo-beta-lactamases (NDM).[7] One recent study conducted has shown prevalence of multidrug resistance as 17%.[8]

Infections caused by these multi drug resistant organisms require timely and appropriate antibiotic therapy to improve patients' survival. Knowledge of antimicrobial susceptibility help clinicians in writing appropriate antibiotics hence decreasing chances of antibiotic resistance. Effective treatment of patients with UTIs commonly relays on the identification of the type of organisms and the selection of an effective antibiotic agent to the organism in question.

MATERIAL AND METHOD

This study was conducted at Medical Unit II, Jinnah Postgraduate Medical Centre, Karachi from 5th September 2016 to 5th March 2017. Approval of ethical review committee of the institution was taken before commencement of the study. Patients were enrolled from Medical Unit II, Jinnah Postgraduate Medical Centre, Karachi. After explaining the procedure informed consent was taken. Patients with UTI diagnosis as per operational definition between age group of 25-75 years were included. Patients who had concurrent other sever illness like chronic obstructive pulmonary disease (COPD), cerebrovascular accident (CVA), metabolic acidosis, and sepsis were excluded. The investigator collected the data on prescribed questionnaires which included baseline characteristics of patients.

Urine sample was obtained from the study subjects using a wide mouth sterile container. All the urine samples were transported to the laboratory and were processed immediately. Urine specimens were investigated by direct microscopy for white blood cell (WBC) counting. For colony count, urine samples were cultured according to surface streak procedure using calibrated loops for semi-quantitative method. The plates were incubated in aerobic conditions at 37^{O}C for 24-48 hours. The result of equal or more than 105 CFU/ml was considered as positive UTI and less than 102 CFU/ml was interpreted as negative UTI. Results of 102-104 CFU/ml was repeated. A total of 108 patients with positive UTI were included in this study after fulfilling inclusion/exclusion criteria. Further testing for antimicrobial resistance was carried out. Results in the form of outcome variable i-e multidrug resistance were noted in proforma. Suitable antibiotic treatment was initiated. Patients

remained admitted till recovery.

Antimicrobial resistance testing

To evaluate antimicrobial resistance of isolates, Kirby-Bauer's Disk diffusion method was done according to Clinical Laboratory and Standards Institute (CLSI; formerly National Committee for Clinical Laboratory Standards) criteria. The following antimicrobial agents were used in this study: Ampicilin; Cephalosporin; Ceftriaxone; Nitrofurantoin; Erythromycin; Norfloxacin; Gentamicin; Vancomycin; Sulfamethoxazole-trimethoprim; Chloramphenicol. Bacterial suspensions was obtained from overnight cultures. The turbidity of each bacterial suspension was adjusted equivalent to a no. 0.5 McFarland standard and then inoculated on Mueller- Hinton agar (Oxoid, UK). Diameter of inhibition zones were measured after incubation at 35ºC for 18-24 hours, and data was reported as resistant if inhibition zone is > 2mm.

Collected data were entered and analyzed using SPSS 21. Mean ± standard deviation (SD) was calculated for age, duration of disease and duration of hospital stay. Frequency and percentage were calculated for sex, type of infection (nosocomial/ nonnosocomial), diabetes mellitus, type of organism (Enterobactersp, E. faecalis, E. coli, Klebsiellasp, P. mirabilis, P. vulgaris, Providenciasp, P.aeruginosa, S. aureus, S. epidermidis) and outcome variable i.e multidrug resistance.

Effect modifiers were controlled through stratification of age, sex, duration of disease, duration of hospital stay and DM, and outcome variable MDR. Chi- square/Fisher Exact test was applied to see the effect of these on outcome variable. P≤ 0.05 was taken as significant.

RESULTS

Hundred and eight patients fulfilling the inclusion criteria were included in this study. The mean ± standard deviation age of study population was 47.92± 12.349 years.

Table 1. Frequency of various organisms cultured

Organism	Number	Percent
E. coli	39	36.1%
E. faecalis	16	14.8%
Enterobactersp	12	11.1%
S. epidermidis	10	9.3%
P. mirabilis	09	8.3%
S. aureus	9	8.3%
Providenciasp	7	6.5%
Klebsiellasp	7	6.5%
P valgurus	6	5.6%
P.aeruginosa	5	4.6%

On analysis of demographics data it was observed 39 (36.1%) were below 40 years of age & 69 (63.9%) were of age 40 years and above. 60 (55.6%) were males and 48 (44.4%) were females (FIG II). 35 (32.4%) patients had DM (FIG III). 42 (38.9%) had Nosocomial infection. 79(73.1%) duration of disease less than 3 days. 64 (59.3%) had hospital stay less than 5 days.

Table 2. Association of cultured organism and MDR

Variable	MDR		P value
	Positive	Negative	
E. Coli			
Yes	21	18	0.000
No	08	61	
E.faecalis			
Yes	04	12	0.563
No	25	67	
Enterobactersp			
yes	02	10	0.322
No	27	69	
S. Epidermidis			
Yes	01	09	0.191
No	28	70	
P. mirabilis			
yes	02	07	0.547
No	27	72	
S. aureus			
Yes	03	06	0.453
No	26	73	
Providenciasp			
Yes	01	06	0.393
No	28	37	

Klebsiellasp			
Yes	01	06	0.393
No	28	73	
P valgurus			
Yes	01	05	0.487
No	28	74	
P.aeruginosa			
Yes	02	03	0.407
No	27	67	

Table 3. Effect of demographics on MDR

Variable	MDR		P value
	Positive	Negative	
Age			
Less than 40 years	10	29	0.501
40 years and above	19	50	
Gender			
Male	15	45	0.349
Female	14	43	
Diabetes Mellitus			
Yes	09	26	0.251
No	20	53	
Duration of disease			
Less than three days	21	58	0.549
Three days above	08	21	
Duration of hospital stay			
Less than 5 days	19	45	0.82
Five days and above	10	34	

Frequency of different organisms cultured is shown in Table 1. On analysis of frequency of outcome variable 29 (26.9%) had antimicrobial MDR. Association of various organisms cultured and MDR is mentioned in Table 2. Stratification with respect to age, gender, DM, duration of disease and duration of hospital stay is mentioned in tables 3 .

DISCUSSION

Our study showed that E. coli, E. faecalis, Enterobactersp and S. epidermidis are the main organism cultured in patients with UTI Some studies carried out in the community have also shown that uropathogens such as Escherichia coli.[10] Klebsiella s, Proteus spp and Enterococcus spp represent the main causes of UTI [11,12]

Our study showed that E coli were major organism cultured. E. coli has been indicated as the most frequent uropathogen involved in the community-acquired UTI [13,15] due to the fact of belonging to the normal flora of the human intestine and therefore easily colonizing the urinary tract. There is evidence that Ecoli causing UTI can be sexually transmitted. Study has found Ecoli isolates of patient matching with partners fecal isolate.[16] Community-acquired urinary tract infections are mainly uncomplicated, colonizing preferably the bladder and causing cystitis.[16,17] However, E. coli may ascend through the ureters to the kidneys and cause more severe infections such as pyelonephritis.[16,17] The bacterium Pseudomonas aeruginosa is emerging as an opportunistic pathogen of UTI in the community and has been associated to 10.7 - 25% of cases.[18,19]

Although E. coli was the most frequent uropathogens implicated in community-acquired UTI (being implicated in more than 30% of all the UTI), as frequently detected in other studies.[20] othse studies have found a significant differences in cases of other bacteria causing UTI.

Contrary to other studies, S. aureus was the 5th most frequent uropathogens involved in the UTI. Even though S. aureus has been associated to hospitalized patients that have undergone catheterization and may be associated to urinary tract infections.[21,22] this bacterium has appeared with high frequency in the community in individuals who were not hospitalized or underwent medical procedures such as dialysis, surgery or catheters. This can be seen in Especially in patients with atopic dermatitis because their microbial flora is altered and who are usually colonized by S. aureus. These individuals serve as major vectors for its transmission.[23,24] In 1997 it was found that 29% of healthy adults outside the hospital environment are colonized by MRSA. Today, it is known that

this value increased to 74%.25 Community-associated MRSA (CA-MRSA) is caused by strains of S. aureus different from those found in the hospital environment. Some studies have shown that CA-MRSA has high potential to become endemic in the community and that this will have a significant impact on the control of MRSA in hospitals [26-28]. Portugal is one of the European countries with MRSA rates higher than 50%[25] which may explain the higher frequency of this bacterium in UTI at the community level relatively to other countries. Staphylococcus saprophyticus, according to the literature has been the second most common cause of uncomplicated UTI, causing 5-10% of the UTI, [29,30] but in this study S. saprophyticus was not among the most implicated bacteria in UTI.

Even though it has been stated that factors such as age might influence the aetiology of urinary tract infection,[31,32] in this study these factors did not cause significant differences among the bacteria responsible for these infections in the different age groups when all samples were considered.

Although E. coli was responsible for more than 30% of the UTI, its antimicrobial resistance was significantly higher than that presented by the other bacteria less implicated in UTI.

In a study conducted on the antimicrobial resistance of pathogens implicated in uncomplicated UTIs patient conducted in nine European countries and Brazil, E. coli showed high resistance to the sulfonamide (29.4%) and reduce resistance to nitrofurantoin (1.6%) and to fluor oquinolone ciprofloxacin (8.1%).[33]

CONCLUSION

Antimicrobial multidrug resistance is not uncommon in patients with Urinary tract infection. E.coli was frequently cultured organism and was significantly associated with antimicrobial MDR.

REFERENCES

1. Simmering JE, Tang F, Cavanaugh JE, Polgreen LA, Polgreen PM. The Increase in Hospitalizations for Urinary Tract Infections and the Associated Costs in the United States, 1998-2011. Open Forum Infect Dis. 2017;4(1):ofw281.

2. Ullah A. Prevalence of symptomatic urinary tract infections and antimicrobial susceptibility patterns of isolated uropathogens in kohat region of Pakistan. MOJ Biol Med [Internet]. 2018 [cited 2020 Nov 7];3(2). Availablefrom: https://medcraveonline.com/MOJBM/prevalence-of-symptomatic-urinary-tract-infections-and-antimicrobial-susceptibility-patterns-of-isolated-uropathogens-in-kohat-region-of-pakistan.html

3. Zubair KU, Shah AH, Fawwad A, Sabir R, Butt A. Frequency of urinary tract infection and antibiotic sensitivity of uropathogens in patients with diabetes. Pak J Med Sci. 2019 Dec;35(6):1664–8.

4. Ganesh R, Shrestha D, Bhattachan B, Rai G. Epidemiology of urinary tract infection and antimicrobial resistance in a pediatric hospital in Nepal. BMC Infect Dis. 2019 May 14;19(1):420.

5. Khoshnood S, Heidary M, Mirnejad R, Bahramian A, Sedighi M, Mirzaei H. Drug-resistant gram-negative uropathogens: A review. Biomed Pharmacother. 2017. 94:982–994.

6. Khawcharoenporn T, Vasoo S, Singh K. Urinary tract infections due to multidrug resistant Enterobacteriaceae: prevalence and risk factors in a Chicago emergency department. Emergency Medicine International. 2013; doi:10.1155/2013/258517.

7. Kumarasamy KK, Toleman MA, Walsh TR, Bagaria J, Butt F, Balakrishnan R, et al. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and

epidemiological study. Lancet Infect Dis. 2010 Sep;10(9):597–602.

8. Sanchez GV, Baird AMG, Karlowsky JA, Master RN, Bordon JM. Nitrofurantoin retains antimicrobial activity against multidrug-resistant urinary Escherichia coli from US outpatients. J AntimicrobChemother. 2014 Dec;69(12):3259–62.

9. Dehbanipour R, Rastaghi S, Sedighi M, Maleki N, Faghri J. High prevalence of multidrug-resistance uropathogenic Escherichia coli strains, Isfahan, Iran. J Nat SciBiol Med. 2016 Jun;7(1):22–6.

10. Mazzariol A, Bazaj A, Cornaglia G. Multi-drug-resistant Gram-negative bacteria causing urinary tract infections: a review. J Chemother Florence Italy. 2017 Dec;29(sup1):2–9.

11. Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. Nat Rev Microbiol. 2015 May;13(5):269–84.

12. Foxman B. Urinary tract infection syndromes: occurrence, recurrence, bacteriology, risk factors, and disease burden. Infect Dis Clin North Am. 2014 Mar;28(1):1–13.

13. Al-Naqshbandi AA, Chawsheen MA, Abdulqader HH. Prevalence and antimicrobial susceptibility of bacterial pathogens isolated from urine specimens received in rizgary hospital - Erbil. J Infect Public Health. 2019 Jun;12(3):330–6.

14. Woldemariam HK, Geleta DA, Tulu KD, Aber NA, Legese MH, Fenta GM, et al. Common uropathogens and their antibiotic susceptibility pattern among diabetic patients. BMC Infect Dis. 2019 Jan 10;19(1):43.

15. Hamdan HZ, Kubbara E, Adam AM, Hassan OS, Suliman SO, Adam I. Urinary tract infections and antimicrobial sensitivity among diabetic patients at Khartoum, Sudan. Ann ClinMicrobiolAntimicrob. 2015 Apr 21;14:26.

16. Thomas M. Hooton. Clinical practice. Uncomplicated urinary tract infection. N Engl J Med. 2012;366:1028–37

17. Schmiemann G, Kniehl E, Gebhardt K, Matejczyk MM, Hummers-Pradier E. The diagnosis of urinary tract infection: a systematic review. DtschArzteblatt Int. 2010 May;107(21):361–7.

18. Cole SJ, Records AR, Orr MW, Linden SB, Lee VT. Catheter-associated urinary tract infection by Pseudomonas aeruginosa is mediated by exopolysaccharide-independent biofilms. Infect Immun. 2014 May;82(5):2048–58.

19. Lamas Ferreiro JL, Álvarez Otero J, González González L, NovoaLamazares L, Arca Blanco A, BermúdezSanjurjo JR, et al. Pseudomonas aeruginosa urinary tract infections in hospitalized patients: Mortality and prognostic factors. PloS One. 2017;12(5):e0178178.

20. Keyhan H, Sedighi S, Mashayekhi B, Fathi M, Mokhtari M. Community Acquired Urinary Tract Infections' Etiological Organisms and Antibiotics Susceptibility Patterns. Nephro-Urol Mon [Internet]. 2017 Sep 7 [cited 2020 Dec 30];9(5). Available from: https://sites.kowsarpub.com/num/articles/62146.html

21. Kitano H, Shigemoto N, Koba Y, Hara T, Seiya K, Omori K, et al. Indwelling catheterization, renal stones, and hydronephrosis are risk factors for symptomatic Staphylococcus aureus-related urinary tract infection. World J Urol. 2020 May 3;

22. Muder RR, Brennen C, Rihs JD, Wagener MM, Obman A, Stout JE, et al. Isolation of Staphylococcus aureus from the urinary tract: association of isolation with symptomatic urinary tract infection and subsequent staphylococcal bacteremia. Clin Infect Dis Off Publ Infect Dis Soc Am. 2006 Jan 1;42(1):46–50.

23. Byrd AL, Deming C, Cassidy SKB, Harrison OJ, Ng W-I, Conlan S, et al. Staphylococcus aureus and Staphylococcus epidermidis strain diversity underlying pediatric atopic dermatitis. SciTransl Med. 2017 Jul 5;9(397).

24. Geoghegan JA, Irvine AD, Foster TJ. Staphylococcus aureus and Atopic Dermatitis: A Complex and Evolving Relationship. Trends Microbiol. 2018 Jun;26(6):484–97.

25. Hassoun A, Linden PK, Friedman B. Incidence, prevalence, and management of MRSA bacteremia across patient populations—a review of recent developments in MRSA management and treatment. Crit Care. 2017 Dec;21(1):211.

26. Shrestha L. B, Baral R, Khanal B. Comparative study of antimicrobial resistance and biofilm formation among Gram-positive uropathogens isolated from community-acquired urinary tract infections and catheter-associated urinary tract infections. Infect Drug Resist. 2019; 12: 957–963.

27. Espadinha D, Faria NA, Miragaia M, Lito LM, Melo-Cristino J, de Lencastre H, et al. Extensive Dissemination of Methicillin-Resistant Staphylococcus aureus (MRSA) between the Hospital and the Community in a Country with a High Prevalence of Nosocomial MRSA. Otto M, editor. PLoS ONE. 2013 Apr 3;8(4):e59960.

28. Takahashi S. MRSA in urology. In GMS; 2018 [cited 2020 Dec 30]. Available from: https://books.publisso.de/publisso_gold/book/52/chapter/78

29. Kuroda M, Yamashita A, Hirakawa H, Kumano M, Morikawa K, Higashide M, et al. Whole genome sequence of Staphylococcus saprophyticus reveals the pathogenesis of uncomplicated urinary tract infection. ProcNatlAcad Sci. 2005 Sep 13;102(37):13272–7.

30. Raz R, Colodner R, Kunin C. M. Who Are You—Staphylococcus saprophyticus? Clinical Infectious Diseases. 2005; 40:896–8.

31. Tenney J, Hudson N, Alnifaidy H, Li JTC, Fung KH. Risk factors for aquiring multidrug-resistant organisms in urinary tract infections: A systematic literature review. Saudi Pharm J SPJ Off Publ Saudi Pharm Soc. 2018 Jul;26(5):678–84.

32. Shabbir M, Iman N, Shah M. Z. Multidrug resistant uropathogens in urinary tract infections and their antibiotic susceptibility patterns. J Med Sci. 2018; 26: (1) 24-27.

33. Gian C. S , Kurt G. N, Henry B, Juan P, Teresita M, Laura G, Anna M. The ARESC study: an international survey on the antimicrobial resistance of pathogens involved in uncomplicated urinary tract infections. Int J Antimicrob Agents. 2009 Nov; 34(5):407-13.

AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author's Full Name	Contribution to the paper	Author's Signature
1	Tasneem Ahsan	Topic selection, Supervision and Review	
2	Shumaila Tahir	Data collection, literature search, paper writing, Statistical Analysis	
3	Syeda Anjala Tahir	Literature Search, Review	
4	Haseeb Ahmed Batti	Literature search, statistical analysis