10.5005/jp-journals-10070-0009

REVIEW ARTICLE

Resistance to Ciprofloxacin in Urinary Tract Infection

[1]Salma Malik, [2]Adesh G Mathur, [3]M Fadil Salmani

ABSTRACT

Introduction: Urinary tract infections (UTIs) are one of the most common infectious diseases worldwide. Approximately >50% of women at least once in their lifetime have suffered from UTI and received antibiotic treatment. Serious UTIs are difficult to treat as it involves a wide array of Gram-positive as well as Gram-negative bacteria. *Escherichia coli (E. coli)* is the primary causative agent implicated in >80% of UTI cases.

Current approach to treatment: A variety of drugs are indicated for the treatment of various clinical forms of UTI. These include nitrofurantoin, cotrimoxazole,fluoroquinolones, some cephalosporins, piperacillin-tazobactam, meropenem, ertapenem etc. Recently various studies have reported ciprofloxacin resistance among *E. coli*, the most common uropathogen.

Review of literature pertaining to ciprofloxacin resistance: The prevalence, factors contributing to resistance and mechanism thereof have been reviewed.Hence, it is necessary to rationalize the use of ciprofloxacin to control the threat of antibiotic resistance.

Conclusion: The incidence of resistance to ciprofloxacin has increased steadily during the past few years. Thus, the empirical use of fluoroquinolones for treatment of UTI should be reconsidered and the drug used only whenthere are clear laboratory tests confirming sensitivity to the drug.

Keywords: Ciprofloxacin resistance, Gram-negative bacteria, Urinary tract infection.

How to cite this article: Malik S, Mathur AG, Salmani MF. Resistance to Ciprofloxacin in Urinary Tract Infection. Journal of Medical Academics 2018;1(1):50-52.

Source of support: Nil

Conflict of interest: None

BACKGROUND

Among all the infectious diseases, UTIs are the second most common after respiratory tract infections. Approximately, 150 million people worldwide are diagnosed with UTI per annum.[1] It is more prevalent in females than in males, with estimates of prevalence suggesting that 40 to 50% of females have at least one clinical episode during their lifetime. The majority of UTIs develop in the normal urinary tract and are therefore termed "uncomplicated" and can affect the lower or upper urinary tract.[1,2]

[1,3]Tutor, [2]HOD

[1-3]Department of Pharmacology, Army College of Medical Sciences, New Delhi, India

Corresponding Author: Adesh G Mathur, HOD, Department of Pharmacology, Army College of Medical Sciences, New Delhi, India, Phone: +919654305664, e-mail: agmathur_pune@yahoo.com

ORGANISMS CAUSING UTI

Uropathogenic *E. coli* (UPEC) causes >80% of community-acquired UTIs, while *Staphylococcussaprophyticus*, *Klebsiella pneumonia*, *Proteus mirabilis,* and *Enterococcus faecalis*are responsible for other infections.[3] A cohort study by Das et al. checking antimicrobial count in urine samples from nursing residents have found that *E.coli* (53.6%) was the major organism followed by *Enterobacteriaceae* (34.8%), *Proteus* (14.6%), *Klebsiella* (13.9%), Providentia (3.7%) and some cases of Gram-positive bacteria such as *Enterococcus* (4.5%) and *Staphylococcus* (4.1%).[4] Furthermore, the cross-sectional study examined urine sample of 32 nursing care facility reported that *E. coli* were the most common organism causing UTI accounting for 69% of positive cases. Other organisms *Klebsiellas* and *Enterobacteriaceae* were found in 12 and 8% cases respectively.[5]

TREATMENT OF UTI

Treatment of UTI with proper antimicrobial therapy can reduce morbidity and mortality due to complications. Choosing the appropriate antimicrobial agent may at times present a therapeutic challenge, but development in the understanding of the pathophysiology of UTI, the introduction of new diagnostic tests, and the availability of new antibacterial agents have allowed physicians to wisely select precise treatment for each patient. Current guidelines followed for treatment of UTI are: for acute uncomplicated cystitis, nitrofurantoin, cotrimoxazole or fluoroquinolones (ciprofloxacin, levofloxacin) are the first-choice drug and cefuroxime is an alternative drug. For acute uncomplicated pyelonephritis, aminoglycosides (amikacin or gentamicin) is first-line therapy, and piperacillin-tazobactam or cefoperazone or ertapenem are administered parenterally as second-line drug therapy. For the treatment of complicated pyelonephritis, Piperacillin-tazobactam or amikacin or cefoperazone are first-line drugs followed by parenteral carbapenems as alternative drugs. For acute prostatitis, first line drugs are doxycycline or co-trimoxazole and Piperacillin-tazobactam or cefoperazone or ertapenem or Imipenem or meropenem are second-line drugs.[6] Fluoroquinolones are the group of drugs having a quinolone ring structure

with fluorine or more fluorine substitutions in the ring structure. These act by inhibiting deoxyribonucleic acid (DNA) synthesis in the bacteria by inhibiting DNA gyrase enzyme in Gram-negative bacteria and topoisomerase IV in Gram-positive bacteria. Ciprofloxacin, one of the fluoroquinolones, frequently prescribed medication for treatment of UTIs as it has good safety profile, marketed as both oral and intravenous formulations, gets easily absorbed after oral administration, has a higher urinary excretion rate and exhibits broad-spectrum activity against gram-negative organisms.[1] Other than UTIs, it is also used for joints, bones and respiratory tract infections and chronic infections such as diarrhea, anthrax, and intra-abdominal infections.[7]

CIPROFLOXACIN RESISTANCE

Due to wide usage of ciprofloxacin for treatment of UTIs, its resistance against uropathogens has increased to a great extent. Blaettler et al. reported increased resistance to ciprofloxacin from 1.8 to 15.9% from 1997 to 2007 (ten years period) in Switzerland.[8] Consistent with this, another study reported a five-fold increase in resistance to ciprofloxacin from 2000 to 2010.[9] A Brazilian study documented that E. coli (10%) and K. pneumoniae (19%) were resistant to ciprofloxacin.[10] Furthermore, another study from Brazil reported that 35% of *E. coli* were resistant to ciprofloxacin.[11] A retrospective study conducted for five years 2010-2014 in Brazil reported that 36% of *E. coli* strains were resistant to ciprofloxacin.[12] Recently, a systematic review and meta-analysis compared ciprofloxacin resistance in hospital-acquired and community-acquired UTI and found that there was significantly ($p < 0.001$) increased resistance in a hospital setting in comparison to community-acquired infections.[1] A recent study has reported that out of 130 urinary samples, 46% were ciprofloxacin resistant. Further, these samples were analyzed for susceptibility testing to various generations of fluoroquinolones. It has been reported that there was a decrease in resistance with the use of a newer generation of fluoroquinolones such as 2nd generation (levofloxacin; 79%), 3rd generation (gatifloxacin; 77%) and 4th generation (moxifloxacin; 75%) fluoroquinolones respectively.[2] Various studies have documented resistance pattern of fluoroquinolones (levofloxacin, ciprofloxacin, nalidixic acid, gatifloxacin) in UTI microorganisms. A study by Omigie et al. have reported that nalidixic acid was least potent in preventing UTI with the resistant rate of 51.75% and ciprofloxacin was the most potent with a sensitivity of 91.2% among all UTI pathogens.[13] Another study has found increase resistance with nalidixic acid (71.9%) with ciprofloxacin (41.4%) in UTI patients.[14] On the contrary, results of a study conducted in Mexico patients stated that resistant pattern of various fluoroquinolones as norfloxacin (60.6%), ofloxacin (60.6%), nalidixic acid (56.4%) and ciprofloxacin (55.5%).[15] Furthermore, Kandel et al. reported fluoroquinolone resistant as ciprofloxacin (59%), levofloxacin (60%), ofloxacin (62%), gatifloxacin (58%) and Nalidixic acid (67%) in UTI pathogens.[16]

Increased number of prescriptions also plays an important role in the development of antimicrobial resistance. The previous study analyzed 72 general practice prescriptions and reported increased resistance of 5.5% with 10 prescriptions over a month in comparison to resistance levels of 3% in practices with one prescription per month.[17] A systematic review documented that frequent non-prescription use of antimicromicrobials in some countries such as in Africa (100%), Asia (58%) and Middle East (39%) can lead to the development of resistance.[18] Another study by Dalhoff reported that the Asia-Pacific region has the highest fluoroquinolone resistance tailed by Europe and North America.[19] Further regional analyses found that Asia had the highest pooled ciprofloxacin resistance with a significantly higher resistance in Africa, Asia, and the Middle East combined in comparison to Europe and America.[1]

Another major factor accounting to antibacterial resistance is the use of antibiotics in animals for growth promotion. Globally, widespread use of antimicrobials in food animal production leads to the development of resistance in the bacterial population. Antimicrobials are given to animals for the prevention or treatment of disease. Usually, antimicrobials are given at lower doses for longer duration which contributes to the development of antimicrobial resistance.[20]

Thus, ciprofloxacin resistance among UTI pathogens has emerged rapidly, therefore should be used cautiously for reserved cases followed by a sensitivity test of the microorganisms involved. Infectious Diseases Society of America (IDSA) guidelines mentioned the use of fluoroquinolones only for reserved cases because of the growth of resistant organisms and infection with multi-drug resistant organisms.[21]

MECHANISM OF ANTIMICROBIAL RESISTANCE

There are various mechanisms by which bacteria develop resistance to an antimicrobial agent such as enzymatic degradation of the antibiotic, changes in the site of the action leading to loss of permeability, increase the activity of efflux pump and alterations of the cell permeability.[22] The mechanism for fluoroquinolones resistance includes the reduction in affinity of antibiotic to target site by alteration in chromosomally encoded target gene pairs *gyrA/parC* and *gyrB/parE* encoding subunits A and B of topoisomerase II/IV. Furthermore, decreased

concentration of drug at the target site occurs either due to increased export of drug out of the cell by increasing number of multidrug-resistant (MDR) pump, i.e., AcrAB-TolC or by decreasing entry of drug into the cell by reducing the expression of outer membrane porin OmpF (a water-filled transmembrane channel) or by action of both.[23]

CONCLUSION

Ciprofloxacin is one of the most commonly prescribed fluoroquinolones for the treatment of uncomplicated UTI. However, the incidence of resistance to ciprofloxacin has increased steadily during the past few years. Thus, the empirical use of fluoroquinolones for treatment of UTI should be reconsidered and the drug used only when there are clear laboratory tests confirming sensitivity to the drug.

REFERENCES

1. Fasugba O, Gardner A, Mitchell BG, Mnatzaganian G. Ciprofloxacin resistance in community- and hospital-acquired Escherichia coli urinary tract infections: a systematic review and meta-analysis of observational studies. BMC Infect Dis. 2015;15:545.
2. Gururaju T, Sarojamma V, Ramakrishna V. Prevalence and Fluoroquinolone Resistance Pattern in *Escherichia coli* Isolates of Urinary Tract Infection (UTI) Patients. JKIMSU. 2015 Apr-June;4(2):56-64.
3. Rowe TA, Juthani-Mehta M. Diagnosis and management of urinary tract infection in older adults. Infect Dis Clin North Am. 2014 Mar;28(1):75-89.
4. Das R, Perrelli E, Towle V, Van Ness PH, Juthani-Mehta M. Antimicrobial susceptibility of bacteria isolated from urine samples obtained from nursing home residents. Infect Control Hosp Epidemiol. 2009 Nov;30(11):1116-1119.
5. Sundvall PD, Ulleryd P, Gunnarsson RK. Urine culture doubtful in determining etiology of diffuse symptoms among elderly individuals: a cross-sectional study of 32 nursing homes. BMC Fam Pract. 2011 May;12:36.
6. National centre for disease control National treatment guidelines for antimicrobial use in infectious diseases. 2016. http://pbhealth.gov.in/AMR_guideline7001495889.pdf
7. Naqvi SAR, Roohi S, Iqbal A, Sherazi TA, Zahoor AF, Imran M. Ciprofloxacin: from infection therapy to molecular imaging. Mol Biol Rep. 2018 Oct;45(5):1457-1468.
8. Blaettler L, Mertz D, Frei R, Elzi L, Widmer A, Battegay M, et al. Secular trend and risk factors for antimicrobial resistance in Escherichia coli isolates in Switzerland 1997–2007. Infection. 2009 Dec;37(6):534-539.
9. Sanchez GV, Master RN, Karlowsky JA, Bordon JM. In vitro antimicrobial resistance of urinary Escherichia coli isolates among US outpatients from 2000 to 2010. Antimicrob Agents Chemother. 2012 Apr;56(4):2181-2183.
10. Santana TC, Pereira EM, Monteiro SG, Carmo MS, Turri RJ, Figueiredo PM. Prevalência e resistênciabacterianaaosagentesantimirobianos de primeiraescolhanasinfecções do tratourinário no município de São Luís-MA. Rev Patol Trop. 2012 Oct-Dec;4(4):409-418.
11. Passadouro R, Fonseca R, Figueiredo F, Lopes A, Fernandes C. Evaluation of the antimicrobial susceptibility of community-acquired urinary tract infection. Acta Med Port. 2014 Nov-Dec;27(6):737-742.
12. Reis AC, Santos SR, Souza SC, Saldanha MG, Pitanga TN, Oliveira RR. Ciprofloxacin resistance pattern among bacteria isolated from patients with community-acquired urinary tract infection. Rev Inst Med Trop Sao Paulo. 2016 Jul;58:53.
13. Omigie O, Okoror L, Umolu P, Ikuuh G. Increasing resistance to quinolones: A four-year prospective study of urinary tract infection pathogens. Int J Gen Med 2009 Dec;2:171-175.
14. Alakhali MK, Alzomor AK, Alavvudeen SS, Khan AN, Dawbaa S. Bacterial resistance of antibiotics antibiotics used in urinary tract infection. Asian J Pharm Clin Res 2013;6:87-91.
15. Molina-López J, Aparicio-Ozores G, Ribas-Aparicio RM, Gavilanes-Parra S, Chávez-Berrocal ME, Hernández-Castro R, et al. Drug resistance, serotypes, and phylogenetic groups among uropathogenic Escherichia coli including O25-ST131 in Mexico City. J Infect Dev Ctries 2011 Dec; 5(12):840-849.
16. Kandel SH, El-Hendy AA, Mohamed RR. Prevalence of quinolones resistance among patients with urinary tract infection at Menoufia. Menoufia Med J. 2014;27(2):440-446.
17. Vellinga A, Murphy AW, Hanahoe B, Bennett K, Cormican M. A multilevel analysis of trimethoprim and ciprofloxacin prescribing and resistance of uropathogenic Escherichia coli in general practice. J Antimicrob Chemother. 2010 Jul;65(7):1514-1520.
18. Morgan DJ, Okeke IN, Laxminarayan R, Perencevich EN, Weisenberg S. Non-prescription antimicrobial use worldwide: a systematic review. Lancet Infect Dis. 2011 Sep;11(9):692-701.
19. Dalhoff A. Global fluoroquinolone resistance epidemiology and implictions for clinical use. Interdisciplinary perspectives on infectious diseases. 2012;2012:1-37.
20. Maron DF, Smith TJ, Nachman KE. Restrictions on antimicrobial use in food animal production: an international regulatory and economic survey. Global Health. 2013 Oct;9:48.
21. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al. Infectious Diseases Society of America; European Society for Microbiology and Infectious Diseases. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis. 2011 Mar;52(5):e103-120.
22. Machuca J, Briales A, Díaz-de-Alba P, Martínez-Martínez L, Pascual Á, Rodríguez-Martínez JM. Effect of the efflux pump QepA2 combined with chromosomally mediated mechanisms on quinolone resistance and bacterial fitness in Escherichia coli. J Antimicrob Chemother. 2015 Sep;70(9):2524-252 7.
23. Redgrave LS, Sutton SB, Webber MA, Piddock LJ. Fluoroquinolone resistance: mechanisms, impact on bacteria, and role in evolutionary success. Trends Microbiol. 2014 Aug;22(8):438-445.