Original Article

Nitrofurantoin: An Alternative Therapy for Uncomplicated Cystitis in the Era of Antimicrobial Resistance

Microbiology Section

ASHA PAI K.B., REKHA RAI, SANJEEV H., VIMAL KUMAR KARNAKER, KRISHNA PRASAD M.S.

ABSTRACT

Introduction: *Escherichia coli* have been implicated as the commonest organism causing uncomplicated cystitis. The frequent irrational use of antibiotics has led to an increased prevalence of resistance to commonly used antibiotics like cotrimoxazole, Fluoroquinolones and β-lactams. Alternative antibiotic compounds are needed to treat such infections. This study was conducted to assess the prevalence of antimicrobial resistance among Escherichia coli causing cystitis and evaluate the sensitivity of these strains to nitrofurantoin.

Materials and Methods: Three hundred and thirty two strains of Escherichia coli obtained from 2293 fresh midstream urine samples were included in the study. Antibiotic sensitivity testing was done by Kirby Bauer disc diffusion method according to CLSI guidelines

Results : Seven hundred and thirty six (32.09%) cases showed significant bacteriuria. A significant number of *Escherichia coli* isolates were found to be resistant to ciprofloxacin (72.59%), Norfloxacin (73.49%) and cotrimoxazole (71.38%). Over 90% of the strains were sensitive to nitrofurantoin. Two hundred and seventeen isolates (65.36%) were found to be ESBL producers by phenotypic confirmatory test. The ESBL producing isolates showed a high rate of sensitivity to ertapenem (96.77%), nitrofurantoin (88.94%) and amikacin (83.41%).

Conclusion: We consider that nitrofurantoin is a good alternative antibiotic to treat uncomplicated cystitis caused by antibiotic resistant *Escherichia coli*.

Key Words: Escherichia coli, uncomplicated cystitis, antimicrobial resistance, nitrofurantoin.

KEY MESSAGE

- Uncomplicated cystitis is frequently caused by antibiotic resistant *Escherichia coli*.
- Alternative antibiotic compounds are needed to treat such infections.
- Nitrofurantoin is a good alternative antibiotic.

INTRODUCTION

Symptomatic urinary tract infection (UTI) is one of the most common infections, worldwide. *Escherichia coli* have been implicated as the commonest organism which causes uncomplicated cystitis. Antibiotics are the mainstay of the treatment for these infections. The frequent irrational use of these antibiotics has led to an increased prevalence of resistance to the commonly used antibiotics like cotrimoxazole, fluoroquinolones and β-lactams [1]. Alternative antibiotic compounds are needed to treat such infections. This study was conducted to assess the prevalence of antimicrobial resistance among *Escherichia coli* which causes cystitis and to evaluate the sensitivity of these strains to nitrofurantoin.

MATERIALS AND METHODS

This study was conducted at our teaching hospital from January 2010–December 2010. In-patients and out-patients with a clinical evidence of cystitis as determined by the treating physician were included in the study. Fresh, mid-stream urine (n =2293) was collected aseptically in sterile containers and it was submitted to the clinical microbiology laboratory. The samples which were received were inoculated onto blood agar and Cysteine Lactose Electrolyte Deficient (CLED) agar. After an overnight aerobic incubation at 37°C, the plates showing significant growth as per the Kass count (single species count of more than 10^5 organisms per ml of urine) were processed further and the isolates were identified upto the species level by using standard biochemical tests. 332 strains of *Escherichia coli* which were thus obtained were included in the study. Antibiotic sensitivity testing was done by the Kirby Bauer disc diffusion method according to the CLSI guidelines [2]. The antibiotics which were tested included ciprofloxacin (5 µg), norfloxacin (10 µg), cotrimoxazole (1.25/23.75 µg), nitrofurantoin (300 µg), amikacin (30 µg) and ertapenem (10 µg). The isolates were also tested for the production of extended spectrum beta lactamases (ESBL) according to the CLSI guidelines [2]. Cefotaxime (30 µg), ceftazidime (30 µg) and ceftriaxone (30 µg) discs were used to screen for the ESBL production. The isolates which tested positive by the screening test were subjected to confirmatory test. Ceftazidime (30 µg) and ceftazidime /clavulanic acid (30 µg /10 µg) discs were used for the confirmatory test. The results were interpreted according to the CLSI guidelines [2].

RESULTS

Out of the 2293 urine samples which were received, 736(32.09%) showed significant bacteriuria.

Escherichia coli was the commonest organism (n=332), constituting 45.10%

Out of the 332 isolates, 207(62.34%) were isolated from female patients and 125 (37.65%) from male patients.

The antibiotic susceptibility pattern of *Escherichia coli* is described in [Table/Fig-1].

The antibiotic sensitivity pattern of the ESBL producers and the non-ESBL producers is shown in [Table/Fig-2].

Antibiotic	No. of isolates (%)	
	Sensitive	Resistant
Ciprofloxacin	91 (27.41)	241 (72.59)
Norfloxacin	88 (26.51)	244 (73.49)
Cotrimoxazole	95 (28.62)	237 (71.38)
Nitrofurantoin	302 (90.98)	30 (9.02%)
Amikacin	294 (88.56)	38 (11.44)
Ertapenem	324 (97.96)	8 (2.40)

[Table/Fig-1]: Antibiotic susceptibility pattern of *Escherichia coli*

Antibiotic	No. of strains sensitive (%)	
	ESBL positive n = 217 (65.36%)	ESBL negative n = 115 (34.64%)
Ciprofloxacin	23 (10.59)	68 (59.13)
Norfloxacin	21 (9.67)	67 (58.26)
Cotrimoxazole	41 (18.89)	54 (46.95)
Nitrofurantoin	193 (88.94)	109 (94.78)
Amikacin	181 (83.41)	113 (98.26)
Ertapenem	210 (96.77)	114 (99.13)

[Table/Fig-2]: Antibiotic sensitivity in ESBL positive and ESBL negative strains

DISCUSSION

Antimicrobial resistance is a growing problem of great concern throughout the world. For the treatment of the patients with cystitis, it is important to consider the local resistance patterns of the commonly isolated pathogens. This study provides an update on the sensitivity of *Escherichia coli* to the commonly used antibiotics.

In the 1990s The Infectious Diseases Society of America (IDSA) affirmed cotrimoxazole as a first line agent for the empirical therapy of uncomplicated cystitis in women in regions where the resistance was below 20% [3]. The increased use of cotrimoxazole in the 1990s led to a high level of resistance worldwide. The prevalence of the resistance to cotrimoxazole among uropathogenic *Escherichia coli* now exceeds 65% in some regions of the world [4]. The rates of resistance which have been reported in this study (71.38%) are comparable to those which are reported in the developing countries (69.5% in Madagascar, 67.8% in Senegal and 82% in India) and are much higher than those which have been reported in the developed countries (22.6% in USA, 17.3% in Canada, 21% in Russia and 26% in Spain) [4, 5-9]. The extensive use of cotrimoxazole explains the high selection pressure for the resistant bacteria. The Infectious Diseases Society of America (IDSA) guidelines recommended an alternative therapy with fluoroquinolones, nitrofurantoin or fosfomycin in regions where the cotrimoxazole resistance exceeds 20% [3]. Hence, cotrimoxazole is not recommended for empirical therapy in our region.

In the past few years, fluoroquinolones have been prescribed more frequently for the treatment of uncomplicated cystitis. This has resulted in an increase in the fluoroquinolone resistant *Escherichia coli* infections [10]. The rate of resistance which has been reported in this study (ciprofloxacin-72.59%, norfloxacin-73.59%) is quite high and is comparable to those which are reported by Francesco MA et al (89.9%) and Tankhiwale SS et al. from India (69%) [7, 11]. On the contrary, some studies have reported very low resistance rates to fluoroquinolones (Zhanel GG et al.-5.5%, Stratchounski LS et al 4.5%) [8, 12]. The high fluoroquinolone resistance in our region might be due to the increased fluoroquinolone use over years, which has been necessitated by high cotrimoxazole resistance.

Aminoglycosides are effective against most of the bacteria which cause cystitis. They have a relatively narrow margin of safety between the therapeutic and the toxic concentrations. They exhibit ototoxicity and nephrotoxicity [13]. They have to be administered parenterally, and are therefore not suitable for the treatment of the out-patients. In our study, 88.65 % were sensitive to Amikacin and it was a good choice for treating uncomplicated cystitis, especially in the in-patients.

With the increased use of cephalosporins, the frequency of the ESBL producing strains has increased in recent years. 65.36 % of the isolates were ESBL producers. This was much higher than that which was reported by Tankhiwale SS (18.5%) and Akram M (34.4%) and was comparable to the percentage from the reports from Narayanaswamy A et al (60%) and Mehrgan H. et al. (67.2 %) [7, 14-15, 16]. Previous studies from India have reported the ESBL production to vary from 28% to 84% [11]. Our study reveals that a high percentage of the ESBL producing strains exhibit resistance to cotrimoxazole, ciprofloxacin and norfloxacin.

Carbapenems are the drug of choice for these strains, as these ESBL producers are frequently multidrug resistant [17]. Our study has shown that 3.23% of the ESBL producing strains were resistant to ertapenem, which was congruent to the data which was provided by Eshwarappa M et al (3.9%) and lesser as compared to the data which was provided by Behera B et al (7%) [18,19]. Most of the other studies have reported 100% sensitivity to carbapenems (Khotari A etal, Mody RM et al) [20, 21]. The disadvantages of using carbapenems include their high cost, their parental administration and the emergence of metallobetalactamases in Enterobacteriaceae. We did not screen these resistant isolates for metallobetalactamase production.

Nitrofurantoin has been used for more than five decades for the treatment of uncomplicated cystitis and it was found to remain active against most of the uropathogens, but its popularity was hampered by a recommended seven day dosing regimen and concerns about its efficacy and tolerance. A study which was conducted by Gupta K et al has revealed that, a 5-day course of nitrofurantoin was equivalent clinically and microbiologically to a 3-day course of cotrimoxazole and that it should hence be considered as an effective fluoroquinolone-sparing alternative for the treatment of acute cystitis in women [22]. Nitrofurantoin was found to retain a good amount of sensitivity (90.98%), both against ESBL producers (88.94%) and non-ESBL producers (94.78%) in our study. This could be correlated with the reports by Kashanian et al. (95.6%) , Sire JM et al. (89.9%) and Karlowsky et al (98.3%) [1,6, 23]. The absorption of oral nitrofurantoin is 40-50% and hence, it is enhanced when it is taken with food. Its serum concentrations are very low to detect and its urine concentrations are 50-250mg/ml [24]. The drug has minimal side effects on short course therapy. It can be used for treating uncomplicated cystitis, including the treatment of cystitis during pregnancy when it is clearly indicated [24].

CONCLUSION

The increased prevalence of antimicrobial resistance among *Escherichia coli* limits the therapeutic options considerably. Not only are the most β-lactams no longer active, but the associated co-resistance reduces the options even further. Alternative antimicrobial compounds are needed to treat the infections which are caused by such resistant organisms. We consider that nitrofurantoin is a good alternative antibiotic to treat uncomplicated cystitis which is caused by antibiotic resistant *Escherichia coli*.

REFERENCES

[1] Kashanian J, Hakimian P, Blute M, Wong J, Khanna H, Wise G et al. Nitrofurantoin: the return of an old friend in the wake of growing resistance. *BJU International* 2008; 102: 1634-37.

[2] Clinical and Laboratory Standards Institute: Performance standards for antimicrobial susceptibility testing; seventeenth informational supplement M 100-S17. Approved standard. Wayne, PA, USA, 2007.

[3] Waren JW, Abrutyn E, Hebel JR, Johnson JR, Schaeffer AJ, Stamm WE, et al. Guidelines for the antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. Infectious Disease Society of America (IDSA). *Clin Infect Dis* 1999; 29: 745-58.

[4] Randrianirina F, Soares JL, Fran J, Carod C, Ratsima E. Antimicrobial resistance among uropathogens that cause community-acquired urinary tract infections in Antananarivo, Madagascar. *J Antimicrob Chemother* 2007; 59: 309–12.

[5] Yilmaz N, Agus N, Yurtsever SG, Pullukcu H, Gulay , Coskuner A et al. Prevalence of antimicrobial susceptibility of *Escherichia coli* in out patient urinary isolates in Izmir, Turkey. *Med Sci Monit* 2009; 15(1):61-65.

[6] Sire JM, Nabeth P, Perrier-Gros-Claude JD, Bahsoun I, Siby T, Macondo EA, et al. Antimicrobial resistance in outpatient *Escherichia coli* urinary isolates in Dakar, Senegal. *J Infect Developing Countries* 2007; 1(3): 263-68.

[7] Thankiwale SS, Jalgaonkar SV, Ahamad S, Hassani U. Evaluation of extended spectrum beta lactamase in urinary isolates. *Indian J Med Res* 2004; 120: 553-56.

[8] Stratchounski LS, Rafalski VV. Antimicrobial susceptibility of the pathogens which were isolated from adult patients with uncomplicated, community-acquired urinary tract infections in the Russian federation: two multicentre studies, UTIAP-1 and UTIAP-2. *Int J Antimicrob Agents* 2006; 28(1):S4-S9.

[9] Gobernado M, Valdes L, Alos JI, Garcia-Rey C, Dal-Re R, Garcia-de-Lomas J, et al. Antimicrobial susceptibility of clinical *Escherichia coli* isolates from uncomplicated cystitis in women over a 1-year period in Spain. *Rev Esp Quimioter* 2007; 20:68-76.

[10] Karaca Y, Coplu N, Gozalan A. Cotrimoxazole and quinolones resistance in *Escherichia coli* which was isolated from urinary tract infections over the last 10 years. *Int J Antimicrobial Agents* 2005; 26: 75-77.

[11] Frencesco MA, Ravizalla G, Peroni L. Urinary tract infections in Brescia, Italy: the aetiology of the uropathogens and the antimicrobial resistance of the common uropathogens. *Med Sci Monit*, 2007: 13(6): BRI 36-44.

[12] Zhanel GG. Antibiotic resistance in outpatient urinary isolates: final results from the North American Urinary Tract Infection Collaboration Alliance (NAUTICA). *Int J Antimicrob Agents* 2005; 26:380-388.

[13] Tripati KD. Aminoglycosides. In: Tripati M, Tripati V editors. Essentials of medical pharmacology. New Delhi: Jaypee brothers, 1999; p.730-38.

[14] Akram M, Shahid M, Khan AU. The aetiology and the antibiotic resistance patterns of community-acquired urinary tract infections in the JNMC Hospital Aligarh, India. *Ann Clinl Microbiol Antimicrob* 2007; 6:4.

[15] Narayanaswamy A, Mallika M. The prevalence and susceptibility of extended spectrum beta-lactamases in the urinary isolates of *Escherichia coli* in a tertiary care hospital in Chennai, South India. *Internet Journal of Medical Update* 2011; 6(1):39-43.

[16] Mehrgan H, Rahbar M. Prevalence of extended-spectrum beta-lactamase-producing *Escherichia coli* in a tertiary care hospital in Tehran, Iran. *Int J Antimicrob Agents* 2008; 31(2):147-51.

[17] Gupta K, Sahm DF, Mayfield D, Stamm WE. Antimicrobial resistance among uropathogens that cause community acquired urinary tract infections in women: A nationwide analysis. *Clin Infect Dis* 2001; 33:89-94.

[18] Eshwarappa M, Dosegowda R, Aprameya VI, Khan MW, Kumar SP, Kempegowda P, et al. The clinico-microbiological profile of urinary tract infections in south India. *Indian J Neprol* 2011; 21: 30-36.

[19] Behera B, Mathur P, Das A, Kapil A. The ertapenem susceptibility of extended spectrum β-lactamase-producing enterobacteriaceae at a tertiary care centre in India. *Singapore Med J* 2009; 50(6):628-32.

[20] Kothari A, Sagar V. Antibiotic resistance in pathogens which cause community-acquired urinary tract infections in India: a multicenter study. *J Infect Developing Countries* 2008; 2(5):354-58.

[21] Mody RM, Erwin DP, Summers AM, Carrero HA, Selby SB, Ewell AJ, Moran KA. Ertapenem susceptibility of extended spectrum beta-lactamase-producing organisms. *Annals of Clinical Microbiology and Antimicrobials* 2007; 6:1-5.

[22] Gupta K, Hooton TM, Roberts PL, Stamm WE. Short-course nitrofurantoin for the treatment of acute uncomplicated cystitis in women. *Arch Intern Med*. 2007; 167(20):2207-12.

[23] Karlowsky JA, et al. Thornsberry C, Jones ME, Sahm DF. Susceptibiliy of antimicrobial resistant urinary *Escherichia coli* to fluoroquinolones and nitrofurantoin. *Clin Infect Dis* 2003; 36:183-87.

[24] Garau J. Other antimicrobials of interest in the era of extended spectrum beta-lactamases: fosfomycin, nitrofurantoin and tigecycline. *Clin Microbiol Infect* 2008; 14(Suppl 1): 198-202.

AUTHOR(S):

1. Dr. Asha Pai K.B.
2. Dr. Rekha Rai
3. Dr. Sanjeev H.
4. Dr. Vimal Kumar Karnaker
5. Dr. Krishnaprasad M.S.

NAME OF DEPARTMENT(S)/INSTITUTION(S) TO WHICH THE WORK IS ATTRIBUTED:

Department of Microbiology,
K.S.Hegde Medical Academy, Nityanandanagar,
Deralakatte, Mangalore 575018.
Karnataka, India.

NAME, ADDRESS, TELEPHONE, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Asha Pai K.B. (MBBS, MD)
Assistant professor, Department of microbiology,
K.S.Hegde Medical Academy, Nityanandanagar,
Deralakatte, Mangalore 575018.
Karnataka, India.
Phone: +91-0824-2204490-92
Fax: +91-0824-22014162
E-mail: ashamkamath@gmail.com

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