WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 5, 2124-2132. Research Article ISSN 2277– 7105

STUDY OF NITROFURANTOIN SUSCEPTIBILITY AMONG UROPATHOGENIC BACTERIAL ISOLATES AT A TERTIARY CARE HOSPITAL, UDAIPUR, RAJASTHAN.

Ritu Bhatnagar[1*], Payal Soni[1], Sanjeev Kumar[2], S.K. Mehra[3], Aruna Solanki[4] and Jyoti Tomar[2]

[1]Assistant Professor, Department of Microbiology, Pacific Medical College and Hospital, Udaipur, Rajasthan.

[2]Tutor, Department of Microbiology, Pacific Medical College and Hospital, Udaipur, Rajasthan.

[3]Professor, Department of Microbiology, Pacific Medical College and Hospital, Udaipur, Rajasthan.

[4]Professor and Head, Department of Microbiology, Pacific Medical College and Hospital, Udaipur, Rajasthan.

Article Received on
06 March 2015,

Revised on 29 March 2015,
Accepted on 19 April 2015

***Correspondence for Author**
Dr. Ritu Bhatnagar
Assistant Professor, Department of Microbiology, Pacific Medical College and Hospital, Udaipur, Rajasthan.

ABSTRACT

Introduction: Urinary tract infections (UTIs) are some of the most common infections experienced by humans.[1] Common bacteria associated with community acquired infectons are E.coli, Coagulase negative Staphylococci, Enterococcus fecalis, Staphylococcus aureus etc.[2] As resistance to Fluroquinolones, Cephalosporins and Co-trimoxazole has become more common in uropathogenes, Nitrofurantoin has become an important alternative oral agent for treatment of uncomplicated UTI.[12] **Aim:** to find out the sensitivity pattern of the urinary isolates against different commonly used antimicrobials in UTI with special reference to Nitrofurantoin. **Material and Methods:** The study was performed from July 2014 to December 2014 at tertiary care hospital, Udaipur, Rajastahn, India. Urine sample from Clinically suspected (OPD and IPD) cases were collected. Processing and identification was done as per standard guidelines. Antimicrobial sensitivity testing was performed by Kirby- Bauer disc diffusion method. **Result and Discussion:** Total 498 test samples were analysed. Out of that, in 251 cases bacterial pathogens were isolated. The most common

organisms isolated were Escherichia coli (58.17%) followed by Klebsiella sp. (13.94%), Enterococcus sp. (8.37%), Pseudomonas sp. (6.37%), and Coagulase negative Staphylococcus sp. (6.38%). Only 29 (11.5%) were resistant to Nitrofurantoin among oral antibiotics. **Conclusion:** Nitrofurantoin is a good choice for the treatment of outpatients.

KEYWORDS: Nitrofurantoin, Urinary tract infections, Antimicrobial resistance pattern, Uropathogenic bacteria

INTRODUCTION

Urinary tract infections (UTIs) are some of the most common infections experienced by humans.[1] Neonates, girls, young women, and older men are most susceptible to UTIs. In women, bacterial cystitis is the most common bacterial infection. It is also the most common cause of nosocomial infections in adults.[1]

Common bacteria associated with community acquired infectons are E.coli, Coagulase negative Staphylococci, Enterococcus fecalis, Staphylococcus aureus etc. while Hospital acquired infections are common with bacteria like E.coli, Klebsiella sp., Pseudomonas aeruginosa, enterobacter, proteus sp. etc.[2]

The extensive and inappropriate use of antimicrobial agents has invariably resulted in the development of antibiotic resistance which, in recent years, has become a major problem worldwide.[3]

In patients with suspected UTI, antibiotic treatment is usually started empirically, before urine culture results are available. To ensure appropriate treatment, knowledge of the organisms that cause UTI and their antibiotic susceptibility is mandatory.[4]

Nitrofurantoin is an age old drug to treat uncomplicated UTI.[5-8] The drug works by damaging bacterial DNA, since its reduced form is highly reactive.[9] Nitrofurantion is bacteriostatic at concentration of ≤32 µg/ml but bacteriocidal at heigher concentration (≥ 100 µg/ml). It absorbed rapidly and completely from gastro-intestinal tract after oral administration and 40% excreted unchanged in urine. Average dose of the drug yield concentration of around 200 µg/ml in urine, which makes it bacteriocidal.[10] The drug is contraindicated in renal failure, last trimester of pregnancy and neonates.[11] There is no cross reaction between Nitrofurantoin and other Anti-microbial agents and resistance emerges slowly.[12]

As resistance to Fluroquinolones, Cephalosporins and Co-trimoxazole has become more common in uropathogenes, Nitrofurantoin has become an important alternative oral agent for treatment of uncomplicated UTI.[12]

Aims and Objectives

Objective of the present study was to find out the sensitivity pattern of the urinary isolates against different commonly used antimicrobials in UTI with special reference to Nitrofurantoin.

MATERIAL AND METHODS

The study was performed from July 2014 to December 2014 with suspected patients with signs and symptoms of UTI at tertiary care hospital, Udaipur, Rajastahn, India. Urine sample from Clinically suspected (OPD and IPD) cases were collected. Samples were inoculated on McConkey Agar and Blood agar plates (HIMEDIA) by semi quantitative method and incubated aerobically at 37^{o}C overnight. Plates showing growth suggestive of significant bacteriuria, with colony counts exceeding 10^{5}cfu/ml were subjected to standard biochemical tests for identification and antimicrobial sensitivity testing by Kirby- Bauer disc diffusion method.[26] Interpretation as 'Sensitive' or 'Resistant' was done on the basis of the diameters of zones of inhibition of bacterial growth as recommended by Clinical Laboratory Standard Institute.[25]

RESULT

Total 498 test samples were analysed. Out of that, in 251 cases bacterial pathogens were isolated. The most common organisms isolated were Escherichia coli (58.17%) followed by Klebsiella sp. (13.94%), Enterococcus sp. (8.37%), Pseudomonas sp. (6.37%), and Coagulase negative Staphylococcus sp. (6.38%) as shown in "fig. 1".

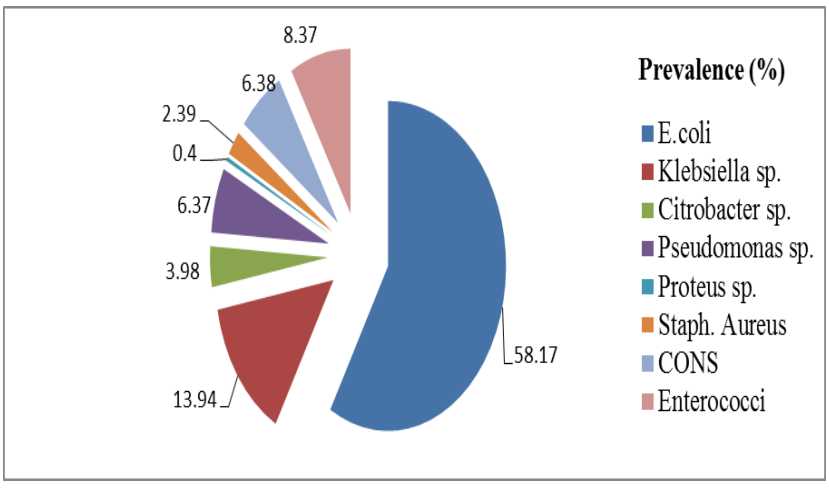

Fig. 1: Prevalance of various urinary bacterial isolates

Among those 25 1isolates, only 29 were resistant to Nitrofurantoin (11.5%) where as resistance to Meropenem was in 37 isolates (14.74%) followed by Piperacillin tazobactum (27.88%), Amikacin (29.48%), Ampicilin-sulbactum (56.57%), Co-Trimoxazole (69.72%), Ciprofloxacin (71.31%) and Ceftazidime (71.31%) as shown in "fig. 2".

Majority of the Nitrofurantoin resistant bacterial isolates were Klebsiella sp.(11 out of 35 i.e. 31.42%) followed by Enterococcus sp. (9.52%) and E.coli (4.79%).

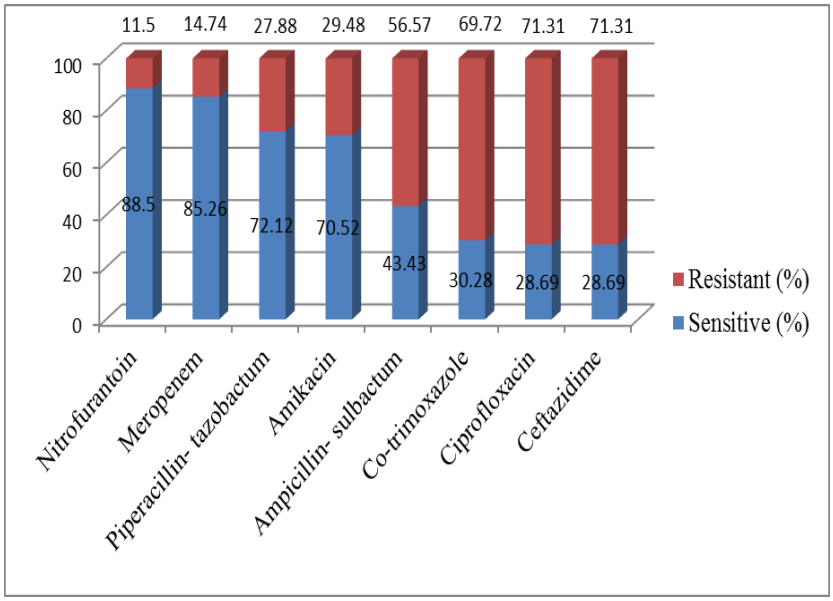

Fig. 2: Antimicrobial resistance (%) of urinary bacterial isolates

E.coli isolates showed high sensitivity to Nitrofurantoin (95.21%), Meropenem (89.05%), Amikacin (82.2%) and Piperacillin-Tazobactum (76.72%). Klebsiella sp. isolates showed high sensitivity to Meropenem (77.15%), Nitrofurantoin (68.58%), Amikacin (60%) and Piperacillin-Tazobactum (60%)

Resistance pattern of other isolated Uropathogenes to commonly used antibiotics is shown in table No. 1 and 2.

There were no other therapeutic options like Fluroquinolones, Ampicillin-sulbactum or Co-trimoxazole to manage the Nitrofurantoin resistant isolates as all of them were resistant to them.

Table no.1: Antimicrobial susceptibility pattern of various organisms (Against Amikacin, Ciprofloxacin, Ceftazidime and Ampicillin- sulbactum)

Organisms	Amikacin		Ciprofloxacin		Ceftazidime		Ampi-sulbactum	
	Resistant	Sensitive	Resistant	Sensitive	Resistant	Sensitive	Resistant	Sensitive
E.coli	26 (17.8%)	120 (82.2%)	110 (75.34%)	36 (24.66%)	101 (69.17%)	45 (30.83%)	77 (52.73%)	69 (47.27%)
Klebsiella sp.	14 (40%)	21 (60%)	27 (77.14%)	8 (22.86%)	24 (68.57%)	11 (31.43%)	23 (65.71%)	12 (34.29%)
Citrobacter sp.	4 (40%)	6 (60%)	7 (70%)	3 (30%)	9 (90%)	1 (10%)	7 (70%)	3 (30%)
Pseudomonas sp.	6 (37.5%)	10 (62.5%)	9 (56.25%)	7 (43.75%)	10 (62.5%)	6 (37.5%)	8 (50%)	8 (50%)
Proteus sp.	0	1 (100%)	0	1 (100%)	1 (100%)	0	0	1 (100%)
Staph. Aureus	2 (33.3%)	4 (66.67%)	3 (50%)	3 (50%)	5 (83.33%)	1 (16.67%)	4 (66.66%)	2 (33.3%)
CONS	4 (25%)	12 (75%)	5 (31.25%)	11 (68.75%)	8 (50%)	8 (50%)	5 (31.25%)	11 (68.75%)
Enterococci	18 (85.7%)	3 (14.3)	17 (80.95%)	4 (19.05%)	21 (100%)	0	18 (85.7%)	3 (14.3)
X^2(df = 7)	40.30		14.13		11.38		11.29	
P value	0.0000011(s)		0.045(s)		0.12(NS)		0.12(NS)	

Table No.2: Antimicrobial susceptibility pattern of various organisms (Piperacillin-tazobactum, Meropenem, Co-trimoxazole, Nitrofurantoin)

Organisms	Piperacillin-tazobactum		Meropenem		Co-trimoxazole		Nitrofurantoin	
	Resistant	Sensitive	Resistant	Sensitive	Resistant	Sensitive	Resistant	Sensitive
E.coli	34 (23.28%)	112 (76.72%)	16 (10.95%)	130 (89.05%)	98 (67.12%)	48 (32.88%)	7 (4.79%)	139 (95.21%)
Klebsiella sp.	14 (40%)	21 (60%)	8 (22.85%)	27 (77.15%)	24 (68.57%)	11 (31.43%)	11 (31.43%)	24 (68.57%)
Citrobacter sp.	3 (30%)	7 (70%)	2 (20%)	8 (80%)	7 (70%)	3 (30%)	1 (10%)	9 (90%)
Pseudomonas sp.	5 (31.25%)	11 (68.75%)	5 (31.25%)	11 (68.75%)	11 (68.75%)	5 (31.25%)	8 (50%)	8 (50%)
Proteus sp.	0	1 (100%)	0	1 (100%)	1 (100%)	0	1 (100%)	0
Staph. Aureus	4 (66.66%)	2 (33.3%)	2 (33.33%)	4 (66.66%)	5 (83.33%)	1 (16.67%)	0	6 (100%)
CONS	2 (12.5%)	14 (87.5%)	0	16 (100%)	9 (56.25%)	7 (43.75%)	0	16 (100%)
Enterococci	8 (38.09%)	13 (61.91%)	4 (19.04%)	17 (80.95%)	21 (100%)	0	2 (9.52%)	19 (90.48%)
X^2(df = 7)	8.18		8.17		9.35		38.54	
P value	0.31(NS)		0.31(NS)		0.22(NS)		0.000002(S)	

Table no.3: Comparison of resistance patterns of uropathogenic E.coli in various studies

Sr. No.	Study title	Study Year	Ciprofloxacin resistance (%)	Co-trimoxazole Resistance (%)	Nitrofurantoin Resistance (%)
1	Shalini et al, U.P., India[1]	2009-2010	30.44	80.40	6.52
2	Assegid Mengistu et al,Namibia[14]	2009-2013	16.82	78.64	6.52
3	Shaifali et al, U.P, India[13]	2012	60.87	39.14	13.05
4	Asrat Agalu Abejew et al[15], Ethiopia	2002-2011	28.3	75.8	10.4
5	Müjde Eryılmaz et al[16], Turkey	2008-2009	15	36	0
6	Lavanya et al[17], Pondicherry, India	2011	--	88	14
7	Present study	2014	75.34	67.12	4.79

Table no.4: Comparison of resistance patterns of uropathogenic Klebsiella sp. in various studies

Sr. No.	Study title	Study Year	Ciprofloxacin resistance (%)	Co-trimoxazole resistance (%)	Nitrofurantoin resistance (%)
1	Shalini et al, U.P., India[1]	2009-2010	31.04	89.66	24.14
2	Assegid Mengistu et al,Namibia[14]	2009-2013	10.49	56.52	23.87
3	Shaifali et al, U.P, India[13]	2012	36.37	18.19	9.1
4	Asrat Agalu Abejew et al[15], Ethiopia	2002-2011	40	65.2	33.33
5	Present study	2014	77.14	68.57	31.42

DISCUSSION

In community and hospital settings the etiology of UTIs and the antimicrobial susceptibility of UTI causing bacteria's have been changing over the years.[1] Over the last decade, the treatment of choice for urinary tract infections (UTIs) has changed from co-trimoxazole to quinolones owing to the rate of resistance to co-trimoxazole and its high level of therapeutic failure.[1] But according to our present study, resistance to ciprofloxacin and ceftazidime is also towards higher side. Comparison of resistance pattern of uropathogenic E.coli and Klebsiella sp. in various studies is shown in Table no. 3 and 4.

In a study conducted by Shalini et al[1], the resistance rates reported among E.coli isolates were: Co-trimoxazole 80.40%; Ciprofloxacin 30.44% and Nitrofurantoin 6.52%. In other

study conducted by Shaifali et al[13], the resistance rates reported among E.coli isolates were: Co-trimoxazole 39.14%; Ciprofloxacin 60.87% and Nitrofurantoin 13.05%. The resistance rates were lower for Ciprofloxacin than those obtained in the present work. Co-trimoxazole resistance rates in comparative studies were variable where as in case of Nitrofurantoin, the resistance rates were comparable to present study. The lower values found in these other studies can be explained by widespread, frequent and injudicious use of antimicrobials.

Since the resistance of uropathogenic strains to antimicrobials has been gradually increasing, it is imperative that prior to deciding on antimicrobial therapy, the antimicrobial susceptibilities of the pathogens causing the UTI should be investigated in order to minimise further resistance development.

Amikacin, Meropenem and Piperacillin-Tazobactum are drugs administered parenterally in the hospital settings to treat severe and complicated UTIs. Hence they are less frequently used and this may contribute to its high sensitivity.[17] We observed that resistance rates were higher among antimicrobials that have been used for long as empirical choice like co-trimoxazole and Ciprofloxacin. This may be due to increased consumption of these antibiotics, self-medication, transfer of resistant isolates and non-compliance with medications.[17]

Nitrofurantoin is a cost effective oral drug with good patient compliance.[18-20] Within its therapeutic range it has no grave adverse effect.[21-24] The present study establishes the fact that majority of the organisms causing UTI are sensitive whether it is a gram positive one (Sensitivity 95.35%) or a gram negative one (Sensitivity 89.58%). So Nitrofurantoin although an old drug emerges as a good alternative drug of choice among oral antibiotics in UTI cases.

Nitrofurantoin can be used in pregnancy espescially in early trimesters whereas opinion about Cotrimoxazole and Ciprofloxacin are still controversial. [10]

CONCLUSION

In conclusion, we can truly affirm that the choice of drugs in the treatment of UTI is quite narrow due to the wide scale resistance to common UTI pathogens. Drugs like co-trimoxazole and ciprofloxacin which were considered as effective against uropathogens, are now rarely prescribed as empirical therapy in areas where resistance rate to theses antibiotics is high. But it is clear that nitrofurantoin is a good choice for the treatment of outpatients. To

tackle the upcoming problems of resistant strains of organisms, nitrofurantoin is again a good choice along with amikacin.

REFERENCES

1. Shalini et al, Study of Antibiotic Sensitivity Pattern In Urinary Tract Infection At A Tertiary Hospital, NJIRM., July- September 2011; 2(3).
2. MIMS' Medical Microbiology, 5th Edition, page no., 237.
3. Goldstein FW. Antibiotic susceptibility of bacterial strains isolated from patients with community-acquired urinary tract infections in France. Multicentre Study Group. Eur J Clin Microbiol Infect Dis., 2000; 19: 112-7.
4. Blondeau JM. Current issues in the management of urinary tract infections: extended-release ciprofloxacin as a novel treatment option. Drugs., 2004; 64(6): 611-28.
5. Zalmanovici Trestioreanu A, Green H, Paul M, Yaphe J, Leibovici L. Antimicrobial agents for treating uncomplicated urinary tract infection in women. Cochrane review. in Cochrane Database Syst Rev., 2010 Oct 6; (10): CD007182.
6. Lutters M, Vogt N. Antibiotic duration for treating uncomplicated, symptomatic lower urinary tract infections in elderly women. Cochrane Database Syst Rev., 2002; 3: CD001535–CD001535.
7. Jellheden B, Norrby RS, Sandberg T. Symptomatic urinary tract infection in women in primary health care. Bacteriological, clinical and diagnostic aspects in relation to host response to infection. Scand J Prim Health Care., 1996 Jun; 14(2): 122–128.
8. Melekos MD, Naber KG. Complicated urinary tract infections. Int J Antimicrob Agents. 2000 Aug; 15(4): 247–256.
9. "Macrobid Drug Label". FDA. Retrieved., 21 April 2014.
10. Goodman and Gilman's The Pharmacological Basis of Therapeutics, 12th edition, chapter., 52: 1475.
11. Essentials of Medical Pharmacology by K. D. Tripathi, 7th edition, chapter., 54: 760
12. Basic and Clinical Pharmacology by Lanze, 12th edition, chapter., 50: 892-893
13. Shaifali et al, Antibiotic susceptibility patterns of urinary pathogens, North American Journal of Medical Sciences , April 2012; Volume 4, Issue 4.
14. Assegid Mengistu et al, A review of Empirical treatment of Urinary Tract Infections based on National Antimicrobial Sensitivity Data, Enliven archive, www.enlivenarchive.org, 2014; volume 1, issue 1.

15. Asrat Agalu Abejew et al, Prevalence and antimicrobial resistance pattern of urinary tract bacterial infections in Dessie area, North east Ethiopia, http://www.biomedcentral.com/1756-0500/7/687.
16. Müjde Eryılmaz et al, Antimicrobial resistance of urinary E.coli isolates, Tropical Journal of Pharmaceutical Research., April 2010; 9(2): 205-209.
17. Lavanya Segar et al, Hemolysin Production and Antibiogram Pattern of Uropathogenic *E. Coli* Isolates from South India, January – February, 2014, Research Journal of Pharmaceutical, Biological and Chemical Sciences, 2014; 225.
18. Cunha BA, Schoch PE, Hage JR Mayo. Nitrofurantoin: in Preferred Empiric Therapy for Community-Acquired Lower Urinary Tract Infections. Clin Proc., 2011 Dec; 86(12): 1243-4.
19. William A. Richards, Egon Riss, Edward h. Kass, maxwell Finland., Nitrofurantoin Clinical and Laboratory Studies in Urinary Tract Infections. AMA Arch Intern Med. 1955; 96(4): 437-450.
20. FishmanN. Antimicrobial stewardship. Am. J Med 2006; 119 6 Suppl 1: S53-61.
21. Veninga CC, Lundborg CS, Lagerløv P, Hummers-Pradier E, Denig P, Haaijer-Ruskamp FM. Treatment of uncomplicated urinary tract infections: exploring differences in adherence to guidelines between three European countries. Drug Education Project Group. Ann Pharmacother., 2000 Jan; 34(1): 19–26.
22. Crider KS, Cleves MA, Reefhuis J, Berry RJ, Hobbs CA,Hu DJ. Antibacterial medication use during pregnancy and risk of birth defects: National Birth Defects Prevention Study. Arch Pediatr Adolesc Med., 2009; 163: 978–85.
23. Drug Safety Update by MHRA. August., 2013; Volume 7, Issue 1, A3.
24. Leão RN, Barreto P, Leão RR, Ribeiro JV. Nitrofurantoin: cause of DRESS syndrome. BMJ Case Rep., 2013.
25. Clinical and Laboratory Standards Institute: Performance standards for antimicrobial susceptibility testing; M100-S22. Wayne, PA: Clinical and Laboratory Standards Institute., 2012.
26. Mackie and McCartney Practical Medical Microbiology, 14th edition, chapter no. 4, page no., 84-90.