

A Study on the Current Trend in Susceptibility Pattern of Uropathogens to Nitrofurantoin in a Tertiary Care Hospital

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Abstract

Introduction: Urinary tract infection (UTI) is the most common health problems in the community as well as in nosocomial set up affecting all age groups from Neonates to Geriatric[1,7]. Widespread use of antibiotics for these highly predictable susceptibility pattern of the common uropathogens has led to the emergence of resistant microorganisms [5]. Nitrofurantoin, a Nitrofuran antimicrobial is a cost effective, well tolerated, oral broad-spectrum bactericidal antibiotic. It acts at multiple site hence is effectively used to treat urinary tract infections (UTIs) caused by *E. coli*, *Klebsiella* sp., *Enterobacter* sp., *Enterococcus* sp. and *Staphylococcus aureus*. [4]. But most *Proteus* species, *Serratia marcescens*, *Morganella morgagni*, *Pseudomonas* species and *Acinetobacter* species are naturally resistant [2,9]. Unfortunately Nitrofurantoin is an underused antimicrobial agent for empirical therapy for community acquired and nosocomial lower UTIs. Hence this study was undertaken to assess the effect of Nitrofurantoin currently against the gram-positive and gram-negative uropathogens.

Materials & Methods: A Crosssectional study was done for one year period (Jan2017-Dec2017) in a tertiary care hospital. A clean catch mid stream urine collected in proper sterile manner were inoculated in CLED agar and incubated at 37^oC for 18-24hrs. The Antibiotic susceptibility testing for the identified uropathogens by standard methodology was done by Kirby Bauer Disc Diffusion Method. The reports of positive urine culture and zone diameter of inhibition of ≤ 14 mm of uropathogens to Nitrofurantoin were recorded for *E.coli*, *Klebsiella* species, *Citrobacter* species, *Enterobacter* species, *Staphylococcus aureus*, CONS and *Enterococcus* species. Phenotypic screening for different beta-lactamase producers like extended spectrum beta-lactamases, Carbapenem resistant *Enterobacteriaceae*, methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant coagulase-negative staphylococci (MRCONS) were also recorded.

Results: Out of 15918 urine samples received and processed, 2880 sample showed growth of uropathogens. Among the isolates, *E.coli* 1288 (44.7%) was the most common followed by *Klebsiella* species 658 (22.8%) and *Enterococcus* species 311 (10.79%). The Antibiotic susceptibility pattern of the isolates to Nitrofurantoin among the GNB were *E.coli* 91%, *Klebsiella* species 78%, *Citrobacter* species 69% and among GPC, *Enterococcus* species 93%, *Staphylococcus aureus* and CONS 100%. Moreover ESBL producing uropathogens were *E.coli* 519 (40%), *Klebsiella* species 241 (36%), *Citrobacter* species 28 (45%). Carbapenem resistant *Enterobacteriaceae* were *E.coli* 105 (8.1%), *Klebsiella* species 30 (4.5%) and *Citrobacter* species 3 (4.8%). Among the GPC, MRSA 7 (41%) and MRCONS 26 (53%).

However ESBL producing *E.coli* 404 (77%), *Klebsiella* species 97 (40%) and *Citrobacter* species 9 (32%) and Carbapenem resistant *Enterobacteriaceae* mainly *E.coli* 10 (9%) were susceptible to Nitrofurantoin.

Among the Gram Positive cocci all the MRSA and MRCONS were 100% susceptible to Nitrofurantoin.

Key words: ESBL, MRSA, Nitrofurantoin

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I. Introduction

Urinary tract infection (UTI) is the most common health problems in the community as well as in nosocomial set up affecting all age groups from Neonates to Geriatric. [1,7] Widespread use of antibiotics for these highly predictable susceptibility pattern of the common uropathogens has led to the emergence of resistant microorganisms. [5] Infections caused by antibiotic resistant pathogens have become a major health problem in recent years as they are very difficult to manage and are of significant concern. They are associated with higher mortality and morbidity. [4] A significant rise in the incidence of Antimicrobial resistance especially MDR uropathogens are well documented.

Nitrofurantoin, a Nitrofuran antimicrobial is a cost effective, well tolerated, oral broad-spectrum bactericidal antibiotic. It acts at multiple site, various steps in carbohydrate synthesis, interfere with the synthesis

of cell wall, bacterial proteins and DNA of both Gram positive and Gram negative pathogens.[1] Hence is effectively used to treat urinary tract infections (UTIs) caused by *E. coli*, *Klebsiella* sp., *Enterobacter* sp., *Enterococcus* sp. and *Staphylococcus aureus*.[4] , but most *Proteus* species, *Serratia marcescens*, *Morganella morgagni*, *Pseudomonas* species and *Acinetobacter* species are naturally resistant.[2,9].

The drug needs activation by bacterial reductase but its not obsolete.[1] Within its therapeutic range it has no grave adverse effects. [1] Nitro-furantoin is preferentially excreted into the lower urinary tract, ie, bladder urine, making it is useful to treat lower UTIs. Nitrofurantoin is useful against *Escherichia coli* and *Enterococci*, the most frequent causes of nosocomial lower UTIs, ie, catheter-associated bacteriuria.[2] Its safe in pregnancy , CRF patients with creatinine clearance of 40ml/min and the first line drug in uncomplicated cystitis and Pyelonephritis.[1,2,3].

But unfortunately Nitrofurantoin is an underused antimicrobial agent for empirical therapy for community acquired and nosocomial lower UTIs. Even among the susceptible uropathogens after extensive use worldwide for more than 50 years, there has been virtually no acquired resistance to nitrofurantoin.[2,3]

Hence this study was undertaken to assess the effect of Nitrofurantoin currently against the gram-positive and gram-negative uropathogens. As the antibiotic sensitivity patterns of the microorganisms are frequently changing, this retrospective analysis was designed to assess the recent antibiotic susceptibility pattern of uropathogens to Nitrofurantoin .

II. Objective Of The Study

To assess the recent *in vitro* susceptibility pattern of nitrofurantoin against uropathogens in a tertiary care hospital.

III. Materials And Methods

3.1 Study type –Cross sectional study

3.1.1 Study material – Reports of positive urine culture and its susceptibility pattern to Nitrofurantoin

3.1.2 Study place – Govt. Stanley Medical College and Hospital.

3.1.3 Study period – January 2017-December 2017 (12months)

3.2 Inclusion criteria

Urine culture positive reports showing pure growth of pathogens. Few colonies to 10^5 CFU/ml according to the isolates with the following criteria were included in the study

All Age Groups

From All Departments

Both Sex

Both Inpatients and Out Patients

3.2.1 Exclusion criteria

Mixed organism

Presence of duplicate isolates

3.3 Methodology

A clean catch mid stream urine collected in proper sterile manner were inoculated in CLED agar and incubated at 37 °C for 18-24hrs. The Antibiotic susceptibility testing for the identified uropathogens by standard methodology was done by Kirby Bauer Disc Diffusion Method. The antibiotics tested for Gram negative bacilli were Ampicillin 10µg, Amikacin 10µg, Gentamicin 10µg, Norfloxacin 10µg, Cefazolin 30µg, Cotrimoxazole 1.25/23.75µg, Cefotaxime 30µg, Piperacillin-Tazobactam, Imipenem 10µg and Nitrofurantoin 300µg. Third line drugs tested for resistance strains were, Meropenem 10µg, Ciprofloxacin 5µg, Colistin 10µg, Tigecycline 15µg [CLSI guidelines 2017] .For Gram Positive cocci, Ampicillin 10µg, Amikacin 10µg, Gentamicin 10µg, Norfloxacin 10µg, Cefazolin 30µg, Cotrimoxazole 1.25/23.75µg, Cefoxitin 30µg, High level gentamicin 120µ, Nitrofurantoin 300µg and Vancomycin 30µg (Enterococci).

The reports of positive urine culture and zone diameter of inhibition of ≤ 14 mm of uropathogens to Nitrofurantoin , were recorded for *E. coli*, *Klebsiella* species, *Citrobacter* species, *Enterobacter* species, *Staphylococcus aureus*, CONS and *Enterococcus* species. The data collected from the registers of Department of Microbiology, Govt Stanley Medical College and Hospital for the period from January 2017-December 2017 (12 months) were analysed.

Phenotypic screening of different beta-lactamase producers like extended spectrum beta-lactamases , Carbapenem resistant *Enterobacteriaceae*, methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant coagulase-negative staphylococci (MRCONS) were also recorded. Data obtained from this study were analyzed using descriptive statistics.

IV. Results

Out of 15918 urine samples received and processed from January 2017 to December 2017,2880 sample showed growth of uropathogens.Among the isolates,E.coli 1288 (44.7%) was the most common followed by Klebsiella species 658(22.8%) and Enterococcus species 311(10.79%).Others were Proteus species 58(2.01%),Citrobacter species 62 (2.15%), Serratia marcescens 2,Acinetobacter species 95 (3.29%),Pseudomonas species 159 (5.52%), Morganella morgagni 1,Staphylococcus aureus 17(0.59%),CONS 49(1.70%),Streptococcus species 9(0.31%),Candida albicans15 (0.52%) and Non albicans Candida 156 (5.41%).(Table-1)(Fig-1)

The Antibiotic susceptibility pattern of the isolates to Nitrofurantoin among the GNB were E.coli 91%,Klebsiella species 78%,Citrobacter species 69% and among GPC Enterococcus 93%,Staphylococcus aureus and CONS 100%.(Table-2)(Fig-2)

Moreover ESBL producing uropathogens were E.coli 519(40%),Klebsiella species 241(36%),Citrobacter species 28(45%).(Table-3) (Fig-3)Carbapenem resistant Enterobacteriaceae were E.coli 105(8.1%),Klebsiella species30(4.5%) and Citrobacter species 3(4.8%). Among the GPC ,MRSA 7(41%) and MRCONS 26(53%).

However ESBL producing E.coli 40(77%),Klebsiella species 97(40%) and Citrobacter species 9(32%) (Table-3) and Carbapenem resistant Enterobacteriaceae mainly E.coli 10(9%) were susceptible to Nitrofurantoin. Among the Gram Positive cocci all the MRSA and MRCONS were 100% susceptible to Nitrofurantoin.

Table-1: List of uropathogens isolated

S.No	Organism	No of Isolates	Percentage
1.	Escherichia coli	1288	44.7
2.	Klebsiella species	658	22.8
3.	Proteus species	58	2.01
4.	Citrobacter species	62	2.15
5.	Serratia marcescens	2	0.06
6.	Morganella morgagni	1	0.03
7.	Pseudomonas species	159	5.52
8.	Acinetobacter species	95	3.29
9.	Staphylococcus aureus	17	0.59
10.	CONS	49	1.70
11.	Enterococcus species	311	10.79
12.	Streptococcus species	9	0.31
13.	Candida albicans	15	0.52
14.	Non albicans candida	156	5.41
	TOTAL	2880	

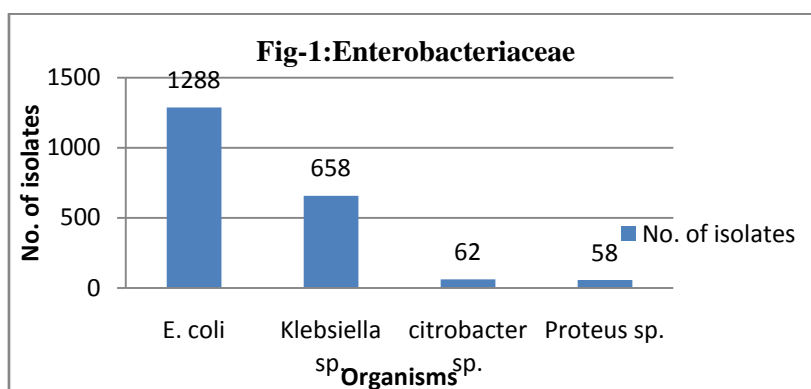


Table-2: Susceptibility pattern of uropathogens to nitrofurantoin

S.No	Organism	No of Isolates	Susceptible to Nitrofurantoin	Percentage
1.	Escherichia coli	1288	1173	91%
2.	Klebsiella species	658	514	78%
3.	Citrobacter species	62	43	69%
4.	Staphylococcus aureus	17	17	100%
5.	CONS	49	49	100%
6.	Enterococcus species	311	291	93%
	TOTAL	2385	2087	87.5%

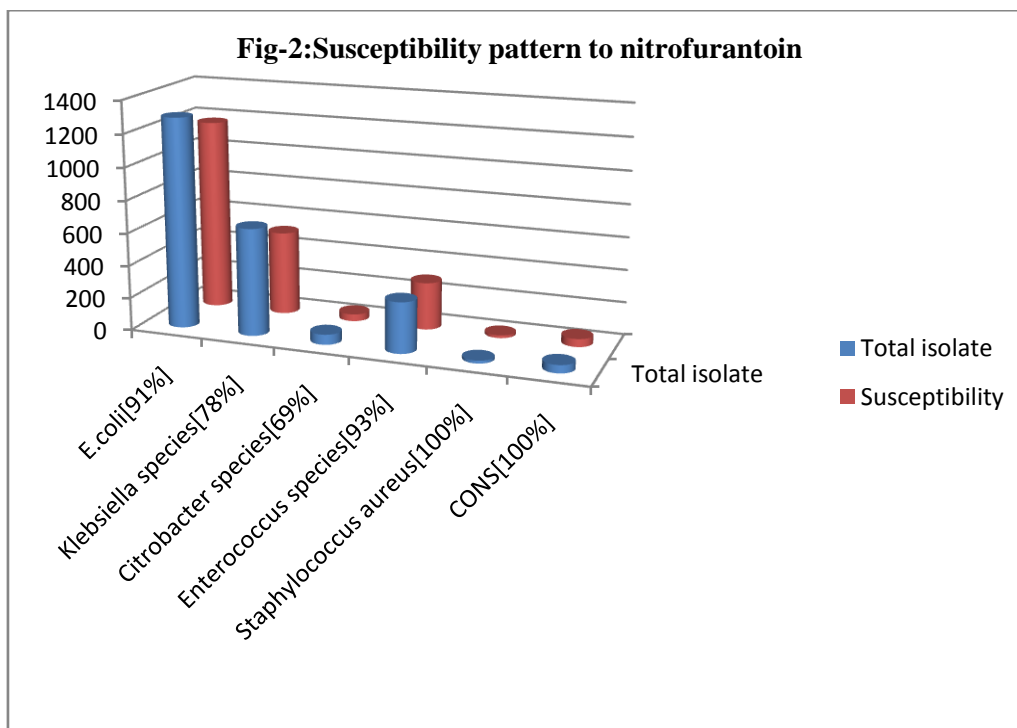
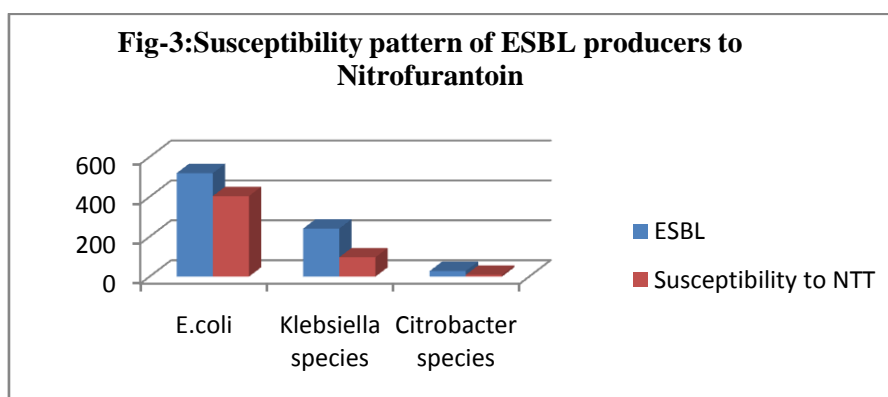


Table-3: Susceptibility pattern of ESBL producing uropathogens to nitrofurantoin

S.No	Organism	Total isolates	ESBL Producer%	Susceptible to Nitrofurantoin	Percentage
1.	Escherichia coli	1288	519 [40%]	404	77.8%
2.	Klebsiella species	658	241 [36.6%]	97	45.3%
3.	Citrobacter species	62	28 [45.1%]	9	32.1%
	TOTAL	2008	788[39.2%]	510	64.7%



V. Discussion

The most common uropathogen was E.coli 44.7% followed by Klebsiella species 22.8% and Enterococcus species 10.79%.(Table-1)(Fig-1). Overall susceptibility to Nitrofurantoin was 87% same as the multicentric study by Kothari and Sagar. Among the enterobacteriaceae, E.coli shows maximum susceptibility of 91% to Nitrofurantoin (Table-2)(Fig-2) same as reported by Jayashree Konar et al as 84%, R.Nalini et al (85%) and Shalini et al from S.India 93%, David et al 94% and Okonko et al 84%, Sunite Ganju et al, 2016, 99%. In India E.coli resistance to Nitrofurantoin ranges from 5-24% [1,3], and in this study it is 9%. All Gram positive uropathogens are still 100% susceptible to Nitrofurantoin.

Other enterobacteriaceae like Klebsiella species 21.8% were isolated and Jayashree Konar et al reported as 30.76% [1] and Shafali et al 9-17%. Among the Klebsiella species, 22% were resistant to Nitrofurantoin, same as reported by Biswas *et al.*, 2006 Dehradun, more than as reported by Liu *et al.*, 2011 (Taiwan) [9], 13.6% and less than reported as Maina *et al.*, 2013 [Kenya], 50%, Kaur *et al.*, 2014 New Delhi reported as 17%

Citrobacter species 30.6% were resistant to Nitrofurantoin.

The ESBL producing E.coli which was 40% in this study more than reported by Balaji et al 2015,34.4%.Among the ESBL producing E.coli, 77% showed susceptibility to nitrofurantoin (Table-3)similar to report of Liu et al(79%)[9]and more than Singh RM et al (65%), Komp Lindgren et al reported rapid and complete killing of ESBL and non-ESBL producing E.coli.[4] Tasbakan *et al.*, and Chen *et al.*,conclude that nitrofurantoin can be considered as an alternative drug in treating *ESBL*producing*E. coli*-related lower UTIs.

Other ESBL producing enterobacteriaceae were Klebsiella species 40% ,as shown by Balaji et al 2015 (27.3%)and citrobacter species 32%.Also 9% were CRE.Among the ESBL producing Klebsiella species,45.3% were susceptible to Nitrofurantoin (Table-3)(Fig-3)same as shown by Maina et al 2013,50% and more than Liu et al 2011 ; 13.6%.[9]

Among the GPC, susceptibility to nitrofurantoin pattern were, Enterococcus 93%,Staphylococcus aureus and CONS 100% same as reported by Subathra et al 2016,100% susceptibility seen in Enterococcus and CONS.[8]

Moreover all the MRSA and MRCONS were susceptible to Nitrofurantoin same as reported by Pulcini et al and Singh RM et al (96%)(Table-2).

The role of Nitrofurantoin in this current trend of drug resistance is significant.

VI. Conclusion

The emergence of antibiotic resistance and the decline in newly developed antibiotics have led to an increasing interest in the treatment and prophylaxis of bacterial UTI with nitrofurantoin.The role of nitrofurantoin is crucial and has become the choice of agent for treating UTIs caused by multi-drug resistant pathogens[1,5]. An agent is deemed unacceptable for empirical treatment where the rate of resistance exceeds 20%.[3] but this study shows only 13%.

Constant surveillance of antibiotic susceptibility pattern will help the Medical practitioners to use safe and effective therapy in the management of UTI.[4]. Proper guidelines,supervision of antibiotic usage and constant information to the Medical practitioners regarding the susceptibility pattern can help to prevent drug resistance and antibiotic misuse. [4]

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