Original article

An analysis on antimicrobial susceptibility pattern of uropathogens with special emphasis on nitrofurantoin in the treatment of uncompl-icated lower UTI

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Abstract:

Background: Urinary tract infection (uti) is the third most common cause of hospital visits for patients in India. The emergence of drug resistance among uropathogens is constantly increasing. The antimicrobial agent nitro-furantoin, a 5 nitro 2 furaldehyde derivative was used extensively to treat the utis previously. The use of this drug has gradually declined in recent years, because of development of many newer drugs in treating utis.

Aim: is to determine the sensitivity pattern of nitrofurantoin among urinary isolates from samples of indoor and outdoor patients at a tertiary hospitalin south india, to find out the common isolates causing uti and to assess the role of nitrofurantoin as an empirical antibiotic in the treatment of uncomplicated uti at this modern era.

Materials and methods: six hundred and twenty six clean catch mid-stream urine samples received in diagno-stic microbiology laboratory of a medical college hospital were taken and processed for this study over a period of six months (june 2011 – november 2011).

Results: The most common bacterial isolates were e.coli (52%) followed by coagulase negative staphylococci (25%), the overall sensitivity of nitrofurantoin for urinary isolates was 85%, highest being cons (100%) and e.coli (98.5%).

Conclusion: Nitrofurantoin showed highest in vitro sensitivity among the most commonly isolated uropath-ogens. Being the cheapest drug with minimal side effects, showing good safety profile and highest sensitivity profile in almost all age groups including pregnant women and children with uti, nitrofurantoin can be prescri-bed for the initial empirical treatment of uncomplicated loweruti and nosocomial uti in place of other drugs such as cotrimoxazole, ciprofloxacin

Key words: Nitrofurantoin, antibiotic sensitivity pattern, e.coli, UTI

Introduction:

Urinary tract infection represents one of the most common diseases encountered in medical practice today and occurring from the neonate to the geriatr-ic age group.[1]the incidence of uti is greater in wom-en as compared to men which is due to anato-mical predisposition of urethra and urothelial mucosal adherence to bacterial mucop-olysaccharide or oth-er host factors.[2] it is estimated that about 20 - 30% of adult women experi-ence uti at least once during their life time.Escherichia coliis the most frequent urinary tract pathogen iso-lated from 50 to 90% of all uncomplicated urinary tract infections. Extensi-ve and inadvertent use of antimicrobial agents, could contribute to antibiotic resistance and change in microbial profile of urinary tract isolates (gales et al., 2005). Since the pattern of antibiotic resista-nce in a wide variety of pathogenic organisms may

vary, periodic evaluation of antibiotic sensitivity p-attern is needed to update information (gupta et al., 2002). Nowadays, the majority of patho-gens isolated from urine are resistant to commonly used anti-biotics and the first choice of an antimicrobial agent for empiric treatment of urinary tract infe-ctions (utis) is not well establish-hed (tseng et al., 2008). So physicians need more information about local susceptibility pattern of uropathogens to select appropriate antibiotic for em-pirical therapy of uncomplicated uti.

Aim & objective of the study is

- To determine the etiologic agents of uti
- To know the antibiotic sensitivity pattern of uropathogens
- To assess the role of nitrofurantoin as an empirical antibiotic in the treatment of uncomplicated uti.

Materials and methods:

Study type and place: a type of prospective diagnostic laboratory study conducted at diagnostic microbiology laboratory, tertiary care hospital, south india

Study period: over a period of six months (june 2011 – november 2011)

Sample size: six hundred and twenty six clean catch mid-stream urine samples

Inclusion criteria: samples of outpatients and inpatients from all age group and both sexes were taken for this study

Exclusion criteria: patients with history suggestive of complicated uti were excluded from this study with stan-dard calibrated loop delivering 0.01 ml of urine was inoculated on macconkey agar plate, blood agar plate and incubated aerobically at 37°c for 18-24 h. After incubation, colonies are counted and if the cfu is more than 10^5, then the isolate was considered as significant and such urine samples were further processed for identifica-tion and antibiogram pattern of bacterial pathogens. Identification of bacterial pathogens was made on the basis of gram reactions, morphology and bioch-emical characteristics. Isolates were tested for sus-ceptibility to nitrofu-rantoin and other standard an-tibiotics by kirby - bauer disc diffusion technique on mueller hinton agar (clsi met-hod, 2011) using readymade antibiotic discs supplied by hi-media ltd, mumbai.

Results:

A total of 626 urine samples were analyzed for isolation and identification of bacterial pathogens as per standard methods. Out of 252 cultural isolates, the most common uropathogen was e.coli – 130 (51.6%), followed by co-ns - 56 (22.2%). The less common isolates were enterobacter species- 2 (0.7%) and pseudomonas aeruginosa – 6 (2.4%). The remaining isolates were klebsiellapn-eumoniae 34 (13.5%), proteus mirabilis 16 (5.6%) and enteric-occi spp 8 (3.2%). (**table 1 & figure 1.1**).

Table 1. Microbial profile of uti and their sensitivity pattern to nitrofurantoin

Isolate	Number (%)	Nit* sensitivity (%)
E.coli	130(51.6)	128(98.5)
Klebsiellapneumoniae	34(13.5)	10(30.0)
Proteus mirabilis	16(05.6)	00(00.0)
Pseudomonas aeruginosa	06(02.4)	00(00.0)
Enterobacterspp	02(0.7)	01(50)
Cons	56(22.2)	56(100)
Enterococci	08(03.2)	08(100)
Total	252(38.7)	211(84.0%)

* - nitrofurantoin

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The sensitivity pattern for nitrofurantoin is given in **table 1. & figure 1.2.**the highest sensitivity was shown by the cons 56/56 (100%) and enterococci 8/8 (100%) among gram positive bacteria.Among gram negative bact-eria, e.coli showed highest sensitivity 128/130 (98.5%). Enterobacterspp 01/02 (50%) showed intermediate sen-sitivity. Only 30% of klebsiellaspp were sensitive to nitrofurantoin. Pseudomonas spp and proteus spp are inher-ently resistant to nitrofurantoin which were accounted for 2-5% of total isolates.the overall sensitivity pattern of uropathogens to all antibiotics are shown in **table 2**. In addition, percentage of esbl producing gram negative ba-cteria (70%)are shown in **table 3**and**figure 3.1. Table 4**and**figure 4.1**depict the percentage of methicillin resist-ant cons strains (30%) amonguropathogens.**Table 5&figure 5.1**shows the nitrofurantoin sensitivity pattern amo-ng drug resistant uropathogens like esbl e. Coli and mr cons. Almost 99% of esbl e.coli and 90% of mr-cons w-ere sensitive to nitrofurantoin.

Table 2: antibiotic sensitvity pattern of uropathogens to all antibiotics

	E.coli N=130	Klebsiella N=34	Proteus N= 16	Pseudomonas N=6	Enterobacter N= 2	Cons N=56	Enterococci N=8
Ampicillin	2	0	0	0	0	3	-
Doxycycline	112	28	11	-	2	13	6
Cephalexin	-	-	-	-	-	0	-
Ceftriaxone	21	11	8	0	1	27	-
Cefotaxime	23	10	9	0	1	26	-
Amoxyclauv	56	18	2	0	0	26	6
Norfloxacin	2	0	0	0	1	9	1
Ciprofloxacin	67	24	14	4	2	25	4
Nitrofurantoin	128	10	-	-	1	56	8
Amikacin	128	30	15	6	2	55	-
Gentamicin	126	28	14	5	2	52	-
Cotrimoxazole	2	0	0	-	2	2	-
Vancomycin	-	-	-	-	-	54	8

Table 3: comparision of esbl and non esbl gram negative isolates (%)**

Isolate	Esbl** strains (%)	Non esbl strains (%)
E.coli (n= 130)	92 (72%)	38 (28%)
Klebsiellasp (n= 34)	29 (85%)	05 (15%)
Proteus sp (n= 16)	09 (56%)	07 (44%)
Pseudomonas sp (n= 6)	02 (33%)	04 (67%)
Enterobacter (n=2)	00 (0%)	02 (100%)
Total (n= 188)	132 (70%)	56 (30%)

**** -extended spectrum beta lactamase**

Table 4: percentage of mr-cons and ms-cons

Isolate	Mr-cons# (%)	Ms-cons$ (%)
Cons(n=56)	17 (30%)	39 (70%)

 # - methicillin resistant coagulase negative staphylococci

$ - methicillin sensitive coagulase negative staphylococci

Table 5: nitrofurantoin sensitivity profile among resistant isolates

Resistant isolate	Nit* sensitivity (%)
E.coli (n=92)	91 (99%)
Klebsiellasp (n= 29)	26 (90%)
Proteus sp (n= 9)	00 (00%)
Pseudomonas sp (n= 2)	00 (00%)
mrcons (n=17)	17 (100%)

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Figure 1.1: distribution of isolates

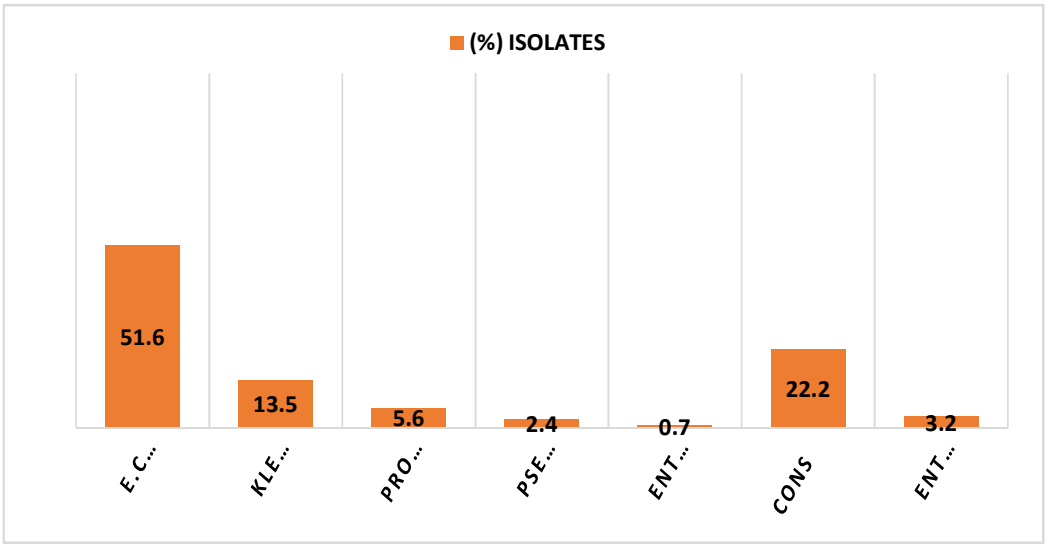

Figure 1.2: percentage of nitrofurantoin sensitivity among uropathogens

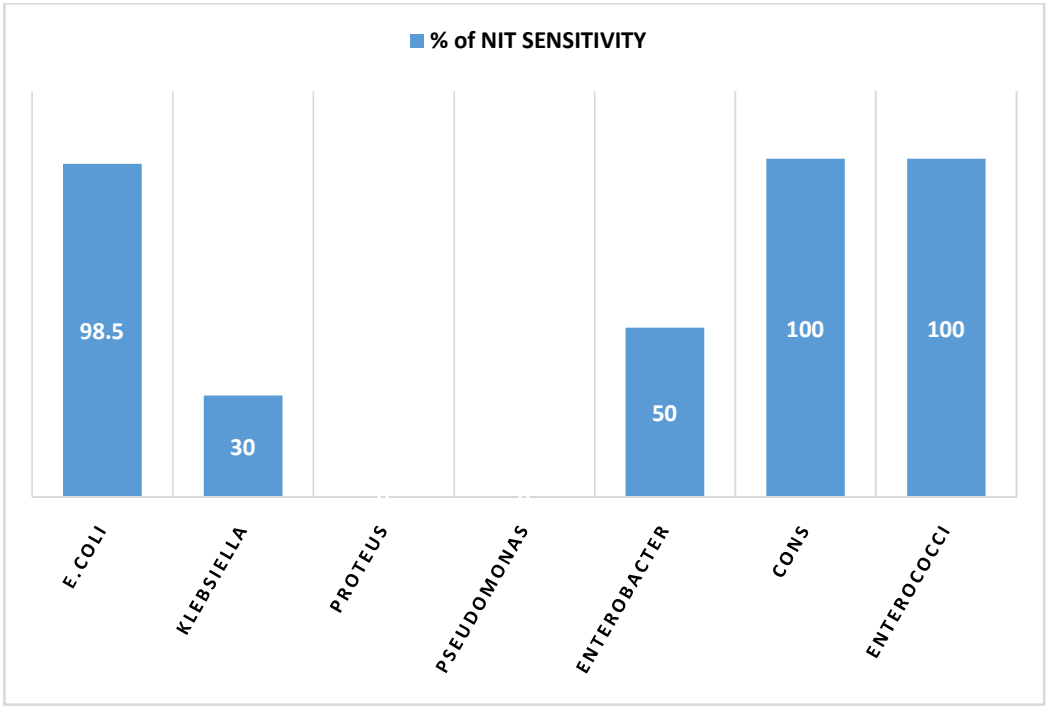

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Figure 3.1: frequency of esbl and non esbl gram negative bacteria in urine culture

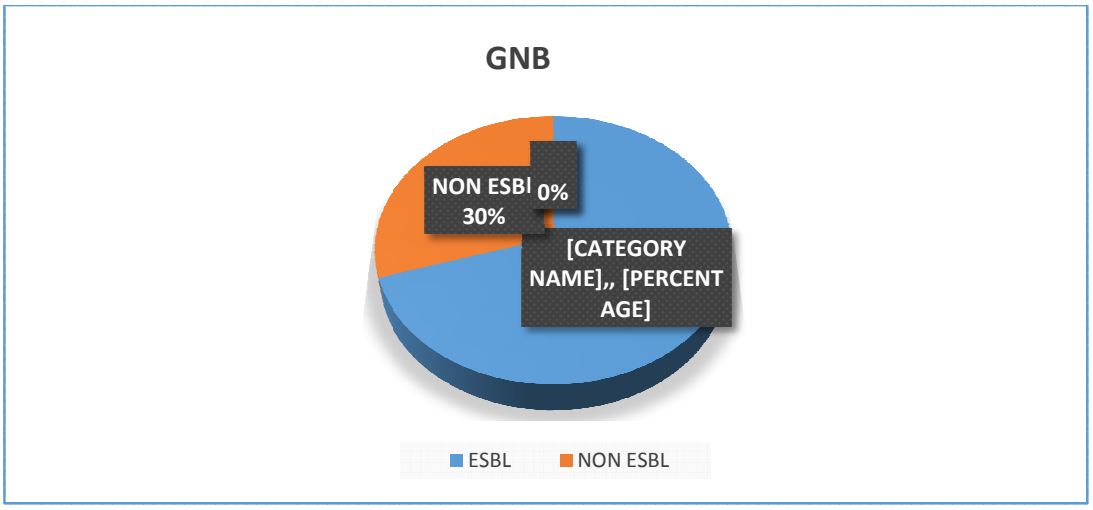


Figure 4.1: frequency of methicillin sensitive and methicillin resistance cons

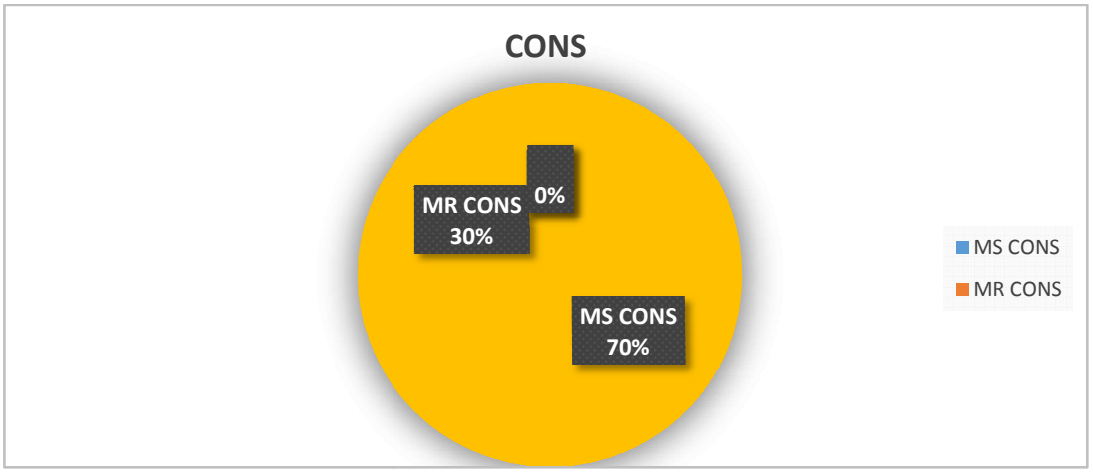
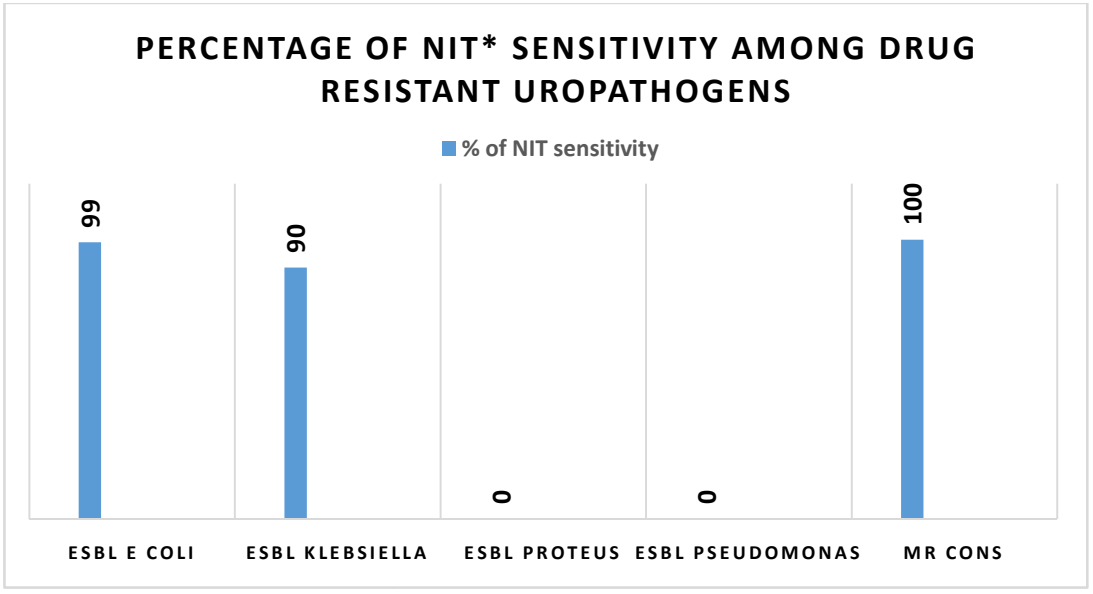


Figure 5.1: percentage of nitrofurantoin sensitivity among drug resistant isolates



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Discussion:

In the present study e.coli was the most common isolate 128/252 (51.6%) among all uropathogens. This was similar to the study conducted by biswas d et al (67.7%) 2006 at dehradun, India and various other studies worldwide.[5, 6] The next common isolate was cons 56/252 (22.2%) followed by klebsiellapneumoniae 34/252 (13.6%). The remaining isolates were proteus mirabilis 16 (5.6%), enterococci spp 8 (3.2%), pseudomonas aeruginosa – 6 (2.4%) and enterobacter species- 2 (0.7%)

Regarding sensitivity pattern of nitrofurantoin, e.coli showed the highest sensitivity pattern (98.5%) for nitrof-urantoin among gram negative bacteria which was supported by all other studies (98.3% to 99.9%) [6, 7, 9]. Among gram positive bacteria, cons and enterococcus species showed 100% sensitivity to nitrofurantoin as had been observed by other studies (99.93% - 100%) [6, 9]. The most suited antibiotic for empirical therapy should have low resistance rates, achieve significant urinary concentrations, be cost-effective, be free of adverse effects and satis-fy patient compliance. Regarding the acceptable resistance rates, the infectious diseases society of america rec-ommends an antibiotic for empirical therapy only if <10-20% of the urinary pathogens are resistant to it.[9] here in our study, nitrofurantoin fulfilled this criteria with acceptable resistance rate (15%) for all isolates alongwith above mentioned advantages.

We studied the overall sensitivity pattern of uropathogens to other commonly used antimicrobial agents. It reve-aled that most of the isolates were sensitive to aminoglycoside antibiotics (98-100%). Next comes the nitrofur-antoin (95-98%) then only the ciprofloxacin. Almost all the isolates were resistant to cotrimaxazole and norflox-acin. These two drugs were extensively used to treat utis in the past.The study results revealed thatprote-usspp and pseudomonas spp were inherently resistant to nitrofurantoin. So, suitable antibiotics for these inhere-ntly resistant strains could beamikacin followed by gentamicin based on our study observation.We also screened for other types of resistances like esbl production in gram negative bacteria and mr-cons in gram positive bact-eria . Extended spectrum beta lactamase production in gram negative bacteria varied from 33% - 85% and met-hicillin resistance in cons isolate was 30%. We noted that nitrofurantoin has got good sens-itivity profile even for these multidrug resistant uropathogens when compared to quinolones and cotrimaxazole. These results are justified by literatures. [18]

Nitrofurantoin is bactericidal in urine at therapeutic doses, and its multiple mechanisms of action have enabled it to retain potent activity against e. Coli despite nearly 50 years of use [11, 12]. E. Coli is still being the most comm.-on cause of community acquired as well as nosocomial lower uti. Nitrofurantoin has got a unique mechanism of action that it inhibits bacterial growth by acting at three different sites of kreb's cycle. The reabsorption of nitro-furantoin is better at acidic ph of urine at 5.5. So the drug is well concentrated in lower urinary tract making it to treat the lower uti. [14-17]

Conclusion:

To conclude, the present study suggests that nitrofurantoin would be a best drug for initial empirical therapy for uncomplicated lower uti in all age groups including pregnant women & children (except in <2 months of age group in children and in last few weeks of pregnancy where it may induce haemolysis). It is also a cost effective drug with low resistance potential, achieves high urinary concentration with limited tissue distribution (not distr-ibuted outside the urinary tract), satisfies

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patient compliance and to be considered as a better alternative for treatment of uti in developing country like India.This study concludes and proves that even after 50years of use nitrofurantoin retains its highest sensitivity prof-ile for uropathogens,especially to e.coli. It is also proved that nitrofurantoin is active against most strains of mu-ltidrug-resistant gram negative bacilli including esbl produc-ing strains. It could be considered as a better oral drug for the treatment of methicillin resistant cons(mrc-ons) isolates and vancomycin resistant enterococci (vre). The activity of other empirical agents like cotrimox-azole and ciprofloxacin are poor against these multi drug resistant bugs. All these mechanisms signify the use of nitr-ofurantoin as a preferred first line empirical antibiotic in the treatment of uncomplicated nosocomial lower uti.

Limitations of the study:

1) Patients with signs suggestive of complicated uti were excluded in this study which demands further surveillance in this aspect
2) Uropathogens like proteus spp and pseudomonas spp are inherently resistant to nitrofurantoin which nee-ds the selection of other suitable antibiotics (amikacin followed by gentamicin in our study) for these strains.

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