ORIGINAL RESEARCH PAPER
Volume-9 | Issue-2 | February-2020 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

THE REVIVAL OF INTEREST IN NITROFURANTOIN

Microbiology

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ABSTRACT

Urinary Tract Infection (UTI) are among the most common bacterial infections that lead patients to seek medical care. Nitrofurantoin is an excellent option for treatment of acute uncomplicated UTI. Aim of the study is to determine the sensitivity profile of Nitrofurantoin in patients with UTI and compare it with sensitivity profile of Norfloxacin and Cotrimoxazole. Overall sensitivity to Nitrofurantoin Norfloxacin and Cotrimoxazole in this study was found to be 67% 27% and 47%. Sensitivity of Escherichia coli to Nitrofurantoin was 84%. Nitrofurantoin is an excellent option for treating acute uncomplicated UTI on OPD basis.

KEYWORDS

Urinary Tract Infection, Nitrofurantoin, resistance, bactericidal

INTRODUCTION

Urinary tract infections (UTIs) are one of the most common health problems both in the community as well as in hospitals[1,2]. Uncomplicated UTIs are responsible for a large number of presentations in general practice, resulting infrequent antibiotic prescriptions and cause significant financial strain on health services[3]. Prevalence increases with age in both men and women[4]. In females, lifetime incidence of UTI is one-in-three (approximately 50 times more than for males).

Risk factors for UTI in women include frequent sexual intercourse, lack of urination after intercourse, use of a diaphragm, use of a spermicide and a history of recurrent urinary tract infections[5,6]. Almost 80% of uncomplicated UTI's are caused by *Escherichia coli*. Other organisms implicated include *Staphylococcus saprophyticus (*5-15%). *Enterococci*, *Klebsiella* species and *Proteus mirabilis* account for a small percentage of overall infections[7].

Nitrofurantoin is an excellent option for treating acute uncomplicated UTI because of its action at multiple sites which includes inhibition of ribosomal translation, bacterial DNA damage, and interference with the Krebs cycle. It is primarily metabolized by bacterial nitroreductases which convert nitrofurantoin into a reactive electrophilic intermediate which targets bacterial ribosomal proteins, causing complete inhibition of protein synthesis[8,9,10]. An estimated 25 million prescriptions for Nitrofurantoin are filled worldwide each year[11].

Nitrofurantoin is available in two crystalline forms: microcrystalline and macrocrystalline. It is marketed as a mixture of both the microcrystalline and macrocrystalline forms (Macrobid: 25 mg macrocrystals plus 75 mg monohydrate form), and also as macrocrystals alone (Macrodantin). Oral bioavailability is 40–50% and is increased when taken with meals [12]. Very low peak plasma level of <2 µg/mL is achieved after 1–4 h of oral administration[13,14]. It is metabolised primarily in renal tissue and is rapidly excreted in the urine with the urinary concentration of nitrofurantoin reaching more than 100 µg/mL (up to 250 µg/mL)[14] making it an ideal choice for treatment of UTI.

Side-effects are few and occur at rates of <0.001%[15]. Haemolytic anaemia can occur in patients with glucose-6-phosphate deficiency. Other side effects include chronic pulmonary reactions, interstitial fibrosis, peripheral neuropathy and hepatic injury but occur only with prolonged medication (>6 months)[9]. Nitrofurantoin is a pregnancy category B drug[16].

Nitrofurantoin has a fairly wide spectrum of activity which includes *E. coli*. It is increasingly used to treat enterococcal infections, including those due to vancomycin resistant enterococci. *Staphylococcus aureus* and *Staphylococcus saprophyticus* are usually susceptible. *Proteus, Serratia* and *Pseudomonas* are intrinsically resistant[17,18]. In cases of catheter-associated UTI, fewer than half of the *Klebsiella* spp., *Enterobacter* spp., and *Serratia* spp. are susceptible. Routine testing is indicated only for *Enterobacteriaceae*, *Staphylococcus* spp. and *Enterococcus* spp.

OBJECTIVE

Objective of this study was to determine the sensitivity profile of Nitrofurantoin in patients of UTI and compare it with sensitivity profile of Norfloxacin and Cotrimoxazole.

MATERIALS AND METHODS

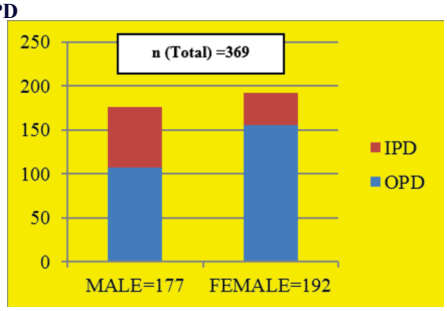
The Cross sectional study was performed in a tertiary care hospital in Western India from July 2016 to May 2017. Consecutive, non-repeat urine samples were obtained from suspected cases of UTI from OPD/IPD patients with signs and symptoms of uncomplicated UTI like discomfort during micturition, fever, urinary urgency, hesitancy and increased frequency. Immunocompromised patients, patients with renal transplantation and patients with any form of catheterization were excluded from the study. Mid stream clean catch urine sample was collected in a sterile universal container. Urine samples plated onto CLED media and incubated for 16-18 hrs. Growth was identified by key tests and biochemical reactions and ABST done by Kirby Bauer disc diffusion method. Antibiotic sensitivity pattern of Nitrofurantoin, Norfloxacin and Cotrimoxazole was recorded as per CLSI 2016 guidelines. Data was analysed statistically.

RESULTS AND DISCUSSION

Out of total 3475 test samples, bacterial pathogens were isolated in 369 cases.

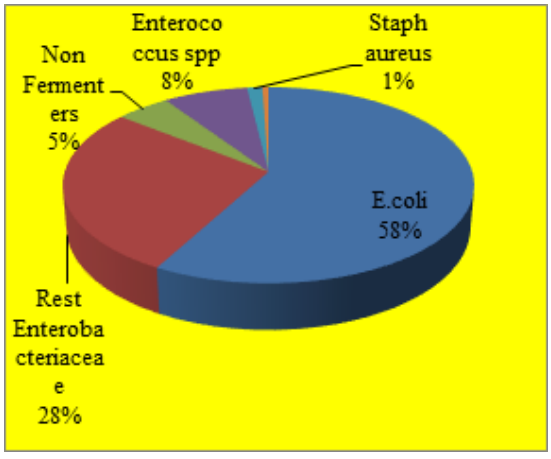
Distribution based on gender and OPD/IPD: Out of the 369 positive cultures from which bacterial pathogens were isolated 177(47.9%) were from male patients with 107(29%) from OPD and 70(19%) from IPD and 192(52.1%) were from female patients with 156(42%) from OPD and 36(10%) from IPD respectively. The distribution of positive cultures based on gender and OPD/IPD is shown in Figure 1.

Figure 1. Distribution of positive cultures based on gender and OPD/IPD



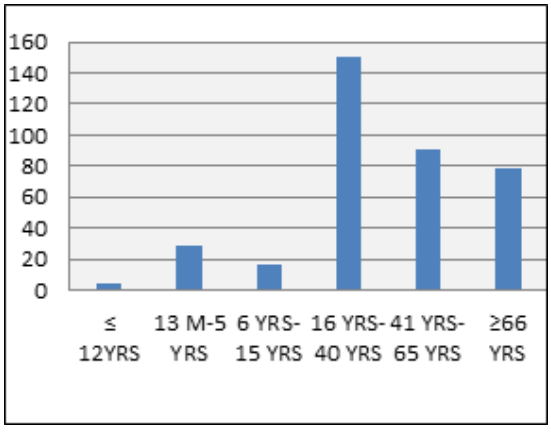
Species wise distribution: Out of 369 positive cultures 334 were Gram negative with majority being *E.coli* which were 214 (58%), other *enterobacteriaceae* were 102 (27.6%) and Non-fermenters comprised of 18 isolates (4.88%). 35 were Gram positive with 28 *Enterococcus* spp (7.6%), 05 being *Staphylococcus aureus* (1.36%) and 02 being CONS (0.5%). Species wise distribution of positive cultures is shown below in Figure 2.

Figure 2. Species-wise Distribution Of Positive Cultures



Age distribution: Of the 369 positive cultures predominant number of positive cultures 150 (40.65%) were from 16Y-40Y age group, followed by 91 (24.66%) which belonged to 41Y-65Y age group and 79 (21.40%) which belonged to >65Y age group. Age wise distribution of positive cultures is shown in Figure 3.

Figure 3. Age-wise distribution of positive cultures



AST pattern:
The AST pattern for Nitrofurantoin, Norfloxacin and Cotrimoxazole is as follows:-

	Sensitive	Intermediate	Resistant
Nitrofurantoin	247 (67%)	23 (6%)	99 (27%)
Norfloxacin	81 (26%)	14 (4%)	217(70%)
Cotrimoxazole	144 (47%)	-	163 (53%)

Figure 4. AST pattern for Nitrofurantoin

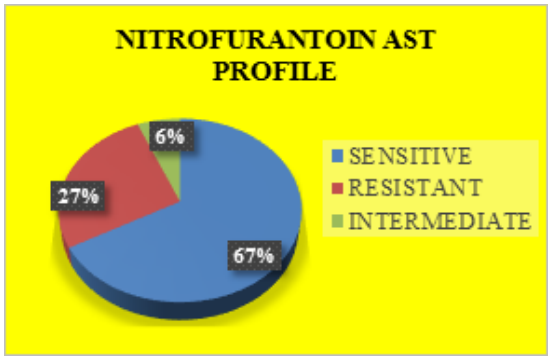


Figure 5. AST pattern for Norfloxacin

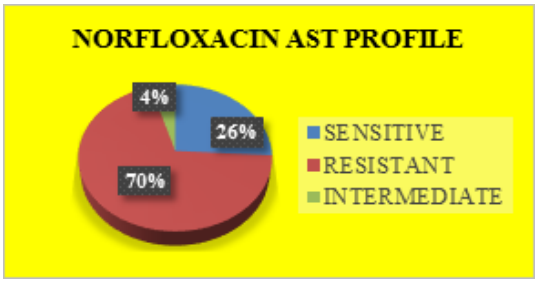
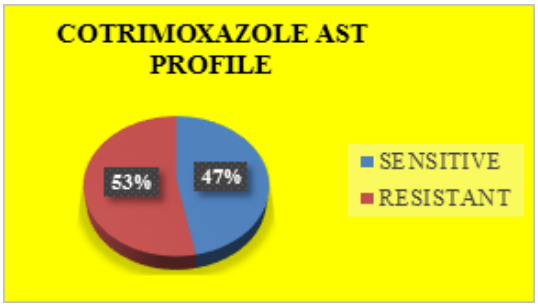
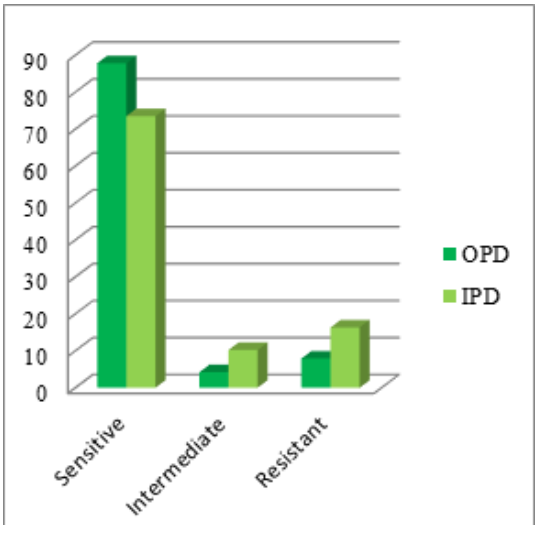


Figure 6. AST pattern for Cotrimoxazole



AST pattern of *Escherichia coli* to Nitrofurantoin: Out of 214 *E. coli* isolated 165 were from OPD and 49 from IPD. The sensitivity of *E. coli* towards Nitrofurantoin was 87.8% and 73.5% for OPD and IPD isolates respectively. The distribution of *E. coli* as per AST profile to Nitrofurantoin for OPD and IPD is shown in Figure 7.

Figure 7. AST pattern for *Escherichia coli* to Nitrofurantoin in OPD and IPD



DISCUSSION:
In our study *E.coli* was found to be the predominant isolate (58%) with similar results in studies of Varma N et al[19] and Gupta V et al[20]. Uropathogenic strains of *E.coli* display a plethora of virulence properties that help them colonize the host mucosal surfaces and bypass host defenses to allow invasion of normally sterile urinary tract[21]. The predominance of females afflicted with UTI was confirmed with the findings of study of Syed et al[22]. A predominance was observed in the 16-65 year age group, similar to study of Salwa Alkhyat H et al[23]. Earlier Cotrimoxazole was preferred widely for treating UTI[24] however the emergence of significant resistance amongst uropathogens has made it unpopular with clinicians across many countries[25]. Fluroquinolones became increasingly used given their ability to concentrate in urine and excellent activity against many uropathogens[24]. Their use for acute uncomplicated UTI was however discouraged by 2011 Infectious Diseases Society of America (IDSA) guidelines[26] citing reasons of emergence of resistance which will have major implications in treatment of other serious conditions like pneumonias and complicated UTIs. However, they still continue to be used extensively Nitrofurantoin has been a suitable and worthy

alternative for treating uncomplicated UTI as it has retained its effectiveness against most uropathogens and other favorable attributes[27]. The threshold of 20% as the resistance prevalence at which the agent is no longer recommended for empirical treatment of acute cystitis is based on expert opinion[26].

The effectiveness of Nitrofurantoin in our study is in accordance with study of D Biswas et al[28]. In a study by Sahni et al[30] Nitrofurantoin resistance was found to be 20%. The corresponding resistance to Nitrofurantoin towards *E.coli* in our study was 10%. The resistance rates observed with fluoroquinolones is in accordance with study of Smita Sood et al[29]. A high rate of resistance is seen in *E. coli* for other oral agents used for out-patient therapy – 63.6–88% against aminopenicillins, 35–75% against ciprofloxacin, and 40–76% against trimethoprim-sulphamethoxazole[29,30,31].

In a multi-centric study, Kothari and Sagar[32] found resistance rates of 24.4% against Nitrofurantoin. A higher rate of nitrofurantoin resistance was reported from Aligarh against *E. coli* with rates of 80%[33].

This wide variation in the rates of resistance may be attributed to the local prescribing practices, thus highlighting the need to use local sensitivity pattern for individual health facilities.

CONCLUSION:

Nitrofurantoin is an excellent option for treatment of acute uncomplicated UTI. It is bactericidal and has a broad spectrum of activity against both Gram positive and Gram-negative bacteria. It's unique multiple mechanism of action hinders development of resistance against it. Nitrofurantoin achieves good concentration in urine, is effective orally, well tolerated and has a low incidence of adverse events and can be used in pregnancy especially in early trimesters whereas opinion about Cotrimoxazole and Ciprofloxacin are controversial. All these characteristics combined with excellent sensitivity profile makes it suitable for use on OPD basis for treatment of uncomplicated UTI.

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