NITROFURANTOIN REVISITED: SUSCEPTIBILITY PATTERN OF UROPATHOGENIC ESCHERICHIA COLI IN A TERTIARY CARE HOSPITAL, SHIMLA, INDIA

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ABSTRACT

Urinary tract infections (UTIs) are a major public health problem and empirical therapy without a pretherapy urine culture is often used. The characteristic features of antibiotics used for empirical therapy should have low resistance rates against the potential pathogens, achieve high urinary concentrations, safe to administer, be cost-effective and satisfy patient compliance. Increasing multidrug resistance in uropathogens has resulted in limited therapeutic choices. Nitrofurantoin, an old antibiotic has received renewed interest. It is effective in treatment of uncomplicated UTIs both in inpatients and outpatients. Our analysis shows that Escherichia coli continues to be the major uropathogen causing UTIs and 99% of the inpatient urinary Escherichia coli isolates are susceptible to nitrofurantoin in our region.

KEY WORDS: Escherichia coli, nitrofurantion, antibiotic susceptibility.

INTRODUCTION

Urinary tract infections (UTIs) are one of the most common infections which can result in serious long term complications if not treated appropriately.[1] Worldwide about 150 million
people are being diagnosed with urinary tract infection every year.\(^2\) Approximately 95% cases of UTIs are bacterial in origin.\(^3\) Amongst the bacteria, \textit{Escherichia coli} (\textit{E. coli}) solely accounts for 85% of community acquired UTIs and 50% of hospital acquired UTIs.\(^4\) Treatment of UTIs in almost 95% of cases is initiated empirically with broad spectrum antibiotics so as to prevent ascent of infection to the upper urinary tract and achieve speedy symptomatic relief.\(^5\) However, the antibiotic susceptibility pattern varies from country to country, region to region, large hospitals to small hospitals and hospital to community.\(^6\) Concurrent antibiotic susceptibility pattern is important to set guidelines for empirical antibiotic therapy and to avoid overuse and misuse of antibiotics. The study aims at analyzing the present susceptibility pattern of \textit{E. coli} isolates from UTI in this region.

**MATERIAL AND METHODS**

This is a retrospective laboratory based study conducted from January 2015 to July 2015. During this period 5924 urine samples were received and processed in the Department of Microbiology, Indira Gandhi Medical College. The majority were clean catch midstream urine samples. All samples were plated within two hours by standardised semiquantitative method on Cystine-Lactose-Electrolyte Deficient agar plates. A single positive culture per patient was included for analysis during this period. Colony counts indicating significant bacteruria, exceeding \(10^5\) cfu/ml were identified by morphology and conventional biochemical tests.\(^7\) Antimicrobial susceptibility testing was done by Kirby- Bauer disc diffusion method on Mueller Hinton Starch Casein Hydrolysate Agar.\(^8\) The antibiotic discs were supplied by Hi-Media laboratories Pvt. Ltd. Mumbai, India. The antibiotics used and susceptibility test results were interpreted according to the Clinical Laboratory Standard Institute (CLSI) 2014 guidelines.\(^9\) The antibiotic discs and their concentrations used for testing were: ampicillin (10\(\mu\)g), amoxiclav (20/10\(\mu\)g), amikacin (30\(\mu\)g), trimethoprim/sulphamethoxazole (co-trimoxazole) (25/23.75\(\mu\)g), nalidixic acid (30\(\mu\)g), norfloxacin (5\(\mu\)g), ciprofloxacin(5\(\mu\)g ), nitrofurantoin (30\(\mu\)g), gentamicin (10\(\mu\)g) cefuroxime (30\(\mu\)g), ceftriaxone (30\(\mu\)g), ceftazidime (30 \(\mu\)g), cephotaxime (30\(\mu\)g), netilmicin (30\(\mu\)g), piperacillin/tazobactam (100/10\(\mu\)g), cefoperazone/sulbactam (75/30 \(\mu\)g) and vancomycin(30 \(\mu\)g).

**RESULTS**

A total number of 5924 samples were received in the department of Microbiology. This included 31% repeat second or the third sample (n= 1862), samples rejected due to faulty
labelling and improper collection 8.1% (n= 484), samples reported sterile 17% (n=1032) and samples reported as mixed growth of contaminants 17.6% (n= 1048). Only a single positive culture per patient was analysed which had only the growth of E.coli. A total of 49.8% (n=747) E.coli pure isolates were identified amongst 1498 pathogenic cultures, out of which 256 were from the indoor patients and 491 were isolated from the outdoor patients. The inpatient E.coli isolates were 99% sensitive to nitrofurantoin, 70% sensitive to gentamicin and 44% sensitive to norfloxacin. Amongst the E. coli urinary isolates from outdoor patients, 60% isolates were sensitive to nitrofurantoin, 34% sensitive to norfloxacin and 28% sensitive to gentamicin. Resistance to cotri-moxazole in admitted patients and outpatient isolates was 43% and 55% respectively. A majority of isolates were resistant to cefuroxime, and ampicillin, being 25% and 22% respectively. Fluoroquinolone resistance was noted in 32% isolates. Resistance to amikacin, ceftazidime, and ceftriaxone was less than 25%. Imipenem resistance was found in <5% of the bacterial isolates.

**DISCUSSION**

*E.coli* is the most predominant uropathogen among bacterial UTIs both in the community and hospital settings. Our study shows that E.coli accounted for 49.8% of all clinically significant urinary isolates and 65.2% of all *Enterobacteriaceae* (n=1144). Similar finding that *E. coli* is the most common uropathogen from patients with UTIs have been reported by Kothari and Sagar.[10] In the first international surveillance programme to determine the susceptibility of the major uropathogens in 16 countries in Europe and Canada, 2525 *E. coli* isolates were cultured from 4734 women.[11] In another study conducted in West Bengal, (2008-2013) India, *Escherichia coli* was the primary uropathogen (67.1%) isolated, followed by *Klebsiella*, (22%), and *Pseudomonas spp* (6%).[12] Kaur et al has shown that *E.coli* was isolated in 45.4% in infants aged less than 1 year.[13] Thus in all ages *E.coli* continues to be the main cause of bacterial UTIs.

The changing susceptibility pattern of uropathogens is concerning in the era of antibiotic resistance. Akram et al detected resistance in 76% of *E. coli* isolates to ampicillin and 75% were resistant to co-trimoxazole.[14] Another study from Rajasthan reports 94.63%, 77.88%, and 74.75% resistance in *E.coli* to nalidixic acid, norfloxacin, and ciprofloxacin respectively.[15] Our study reports resistance to both in the hospital acquired and community acquired strains to the major antibiotics prescribed for treatment of UTI. This shows that resistant strains have spread to the community.
Nitrofurantoin is a urinary antibiotic and solely prescribed in UTIs. It has shown the least resistance to *E. coli*. In our study 99% inpatient and 84% outpatient urinary *E. coli* isolates were sensitive to nitrofurantoin. This is similar to several Indian studies showing that *E. coli* is still susceptible to nitrofurantoin as shown in the Table 1.

**Table 1: *E. coli* Susceptibility Pattern for Nirofurantion in Indian studies**

<table>
<thead>
<tr>
<th>S.No</th>
<th>Author</th>
<th>Year</th>
<th>Nitrofurantoin Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lohiya <em>et al.</em>[16]</td>
<td>2015</td>
<td>100%</td>
</tr>
<tr>
<td>2</td>
<td>Gupta <em>et al.</em>[17]</td>
<td>2015</td>
<td>97%</td>
</tr>
<tr>
<td>3</td>
<td>Nalini <em>et al.</em>[18]</td>
<td>2014</td>
<td>85.19%</td>
</tr>
<tr>
<td>4</td>
<td>Kaur <em>et al.</em>[19]</td>
<td>2014</td>
<td>95%</td>
</tr>
<tr>
<td>5</td>
<td>Shafali <em>et al.</em>[19]</td>
<td>2012</td>
<td>86.95%</td>
</tr>
<tr>
<td>6</td>
<td>Sood and Gupta,[15]</td>
<td>2012</td>
<td>95.96%</td>
</tr>
<tr>
<td>7</td>
<td>Shalini <em>et al.</em>[20]</td>
<td>2011</td>
<td>93.48%</td>
</tr>
<tr>
<td>8</td>
<td>Kothari and sagar,[10]</td>
<td>2008</td>
<td>65.7%</td>
</tr>
<tr>
<td>9</td>
<td>Biswas <em>et al.</em>[21]</td>
<td>2006</td>
<td>90.7%</td>
</tr>
<tr>
<td>10</td>
<td>Mathai <em>et al.</em>[22]</td>
<td>2004</td>
<td>90%</td>
</tr>
<tr>
<td>11</td>
<td>Gupta <em>et al.</em>[23]</td>
<td>2002</td>
<td>85-88%</td>
</tr>
</tbody>
</table>

In our study as well as other studies conducted in other parts of our country the susceptibility to nitrofurantoin is more than 85-100%. Emergence of *extended spectrum β-lactamase (ESBL)* resistant *E. coli* has been noted all over the world. Studies conducted in Rohtak, and Nagpur document 40% and 18.5% of *E. coli* to be *ESBL* producers.[24, 25] Increasing trend in the isolation of *ESBL* producing *E. coli* from 9.52% to 30.08% has been noted in Jaipur over a two and half years study period.[15] At the same time several studies have also shown that *ESBL*-producing *E. coli* isolates are susceptible to nitrofurantoin ranging from 70-95%. In recent surveys in the USA and Canada the rate of resistance to nitrofurantoin was 1.1% among 1,142 outpatient *E. coli* urinary isolates.[26] Similarly in France 1.8% of all urinary *E. coli* isolates were resistant to nitrofurantoin in 2005.[27] Tasbakan *et al.*, and Chen *et al.*, conclude that nitofurantoin can be considered as an alternative drug in treating *ESBL*-producing *E. coli*-related lower UTIs.[28, 29] Microbiological success, defined as a sterile control urine culture was achieved in 51 out of 75 patients (68%) with lower urinary tract infection caused by culture-proven *ESBL*-producing nitrofurantoin-sensitive *E. coli* in the urine.[28] There are limited studies demonstrating the pharmacodynamic properties of nitrofurantoin. In a study rapid and complete killing of *ESBL* and non-*ESBL* strains of *E. coli* in static time kill experiment has been demonstrated.[30]
Nitrofurantoin is a broad-spectrum bacteriocidal antibiotic. Since its discovery in 1952, and its use for more than four decades no clinically significant resistance has developed, as seen with other commonly used antibiotics. This is probably because Nitrofurantoin has multiple sites and levels of action in contrast to antibiotics that attack a single target like ampicillin or two targets like cotrimoxazole. Bacterial nitroreductase enzyme converts nitrofurantoin to highly reactive electrophilic intermediates which non-specifically attack bacterial ribosomal proteins resulting in complete inhibition of protein synthesis\(^{31}\) and cause single-strand breaks in DNA.\(^{32}\)

Nitrofurantoin also has good safety profile and has fewer side effects. It is considered as a good alternative in the treatment of UTI in pregnancy. Nitrofurantoin is recommended as the drug of first choice for the treatment of uncomplicated cystitis and pyelonephritis in women by Infectious Disease Society of America and the European Society for Microbiology and Infectious Disease.\(^{33}\) European Committee on Antimicrobial Susceptibility Testing recommends the use of nitrofurantoin only for uncomplicated UTIs\(^{34}\) The dose recommendations varies from 50 mg three or four times daily to 100 mg twice or four times daily\(^{35}\) However, in ESBL producing \(E\).\(coli\) a longer course of treatment is required.\(^{28,29,35}\)

The rate of nitrofurantoin resistance is lower being around 5-15% as reported in various studies in India since long. However, two studies have documented high resistance 24.4% and 80% in \(E\).\(coli\) conducted in 2007 and 2008.\(^{10,14}\) The wide variation in the rates of resistance could be explained on the basis of local treatment practices. Usually in a tertiary care hospital third generation cephalosporins and fluroquinolones are prescribed. Higher resistance is expected to antibiotics prescribed frequently.

There are some limitations in the study. Since this is a retrospective laboratory based study no clinical data is provided and thus the study does not address issues regarding uncomplicated versus complicated UTIs, community acquired versus hospital acquired UTIs and catheter associated UTIs. \(E\).\(coli\) is the most common uropathogen and changing resistance patterns reduce the safety and efficacy of empirical therapy. Regular periodic monitoring of antibiotic susceptibility is of utmost importance. Despite being used for many years, nitrofurantoin has a good clinical and microbiological efficacy in uncomplicated UTI patients and is the choice of drug for thus the importance of preservation of old drugs cannot be underscored in an era facing lack of new antibiotics.
BIBLIOGRAPHY


