A COMPARISON OF NITROFURANTOIN, FLUOROQUINOLONES AND CO-TRIMOXAZOLE SUSCEPTIBILITY PATTERN AMONG THE UROPATHOGENS IN A TERTIARY CARE HOSPITAL

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ABSTRACT

BACKGROUND
Increasing antibiotic resistance in acute uncomplicated lower urinary tract infection complicates its treatment by increasing patient morbidity and rates of hospitalisation. In the present study, we have aimed at determining the spectrum of gram-negative bacteria causing urinary tract infection; their sensitivities to nitrofurantoin, fluoroquinolones and co-trimoxazole and to compare the sensitivity pattern among different organisms and among outpatients and inpatients.

MATERIALS AND METHODS
We retrospectively studied the susceptibility patterns of gram-negative isolates for 2 yrs. from October 2014 to September 2016 to nitrofurantoin, fluoroquinolones and co-trimoxazole. The results were analysed statistically by χ² test.

RESULTS
Out of the total of 484 gram-negative bacilli isolates from urine, 300 were E.coli, 138 were other Enterobacteriaceae and 46 were non-fermenters.

Overall sensitivity among the gram-negative bacilli to nitrofurantoin was 82.6%, whereas it was 51.6% to fluoroquinolones and 42.3% to co-trimoxazole. E. coli showed 92% sensitivity rate to nitrofurantoin, 52% to fluoroquinolones and 41% to co-trimoxazole. Other Enterobacteriaceae exhibited higher sensitivity rates to nitrofurantoin (81.7%) when compared to fluoroquinolones (67.9%) and co-trimoxazole (51.1%). The non-fermenters showed higher level of sensitivity to fluoroquinolones (54.4%) than to nitrofurantoin (23.9%) and co-trimoxazole (39.1%).

Among the isolates from outpatients, 91.1% were sensitive to nitrofurantoin, 80% to fluoroquinolones and 58.5% to co-trimoxazole. Isolates from the patients admitted to various wards showed higher sensitivity to nitrofurantoin (81.6%) when compared to fluoroquinolones (48.7%) and co-trimoxazole (38.8%). Isolates from the ICU patients exhibited higher level of sensitivity to nitrofurantoin (60.5%) than to fluoroquinolones (36.8%) and co-trimoxazole (28.9%).

CONCLUSION
This study shows that nitrofurantoin is an acceptable empirical treatment for uncomplicated UTI particularly in the outpatient setup.

KEYWORDS
Nitrofurantoin, Fluoroquinolones, Co-trimoxazole, Uropathogens.

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BACKGROUND
Urinary Tract Infections (UTI) affect an estimated 150 million per annum worldwide.¹ Uncomplicated community-acquired urinary tract infections are among the most common infections in women.² About half of all women have at least one UTI during their lifetime.³ The peak incidence of disease occurs between 18-39 years of age.⁴ Approximately, 30%-40% of patients will experience more than one recurrence.⁴

Although, susceptibility patterns have changed over the years, the spectrum of agents causing community-acquired UTI has remained relatively constant. Worldwide, Escherichia coli accounts for 75% to 90% of cases; Staphylococcus saprophyticus accounts for 5% to 15% (particularly in younger women); and Enterococci and other gram-negative bacilli such as Klebsiella species and Proteus mirabilis account for the remaining 5% to 10%.²

Acute uncomplicated lower urinary tract infection (cystitis) is one of the most common and easily cured bacterial infections. However, increasing antibiotic resistance complicates its treatment by increasing patient morbidity and rates of hospitalisation.⁴ During the past two
decades, antimicrobial resistance among uropathogens has increased.\(^5\)

The Infectious Diseases Society of America recommends that physicians obtain information on local resistance rates and that regular surveillance be conducted to monitor changes in susceptibility of uropathogens.\(^1\)

Fluoroquinolones and co-trimoxazole are commonly used for treatment of UTI. In view of the growing resistance rates among the isolates, there is a need to re-evaluate our options for therapy based upon the local resistance rates. This study will focus on the sensitivity pattern of the isolates to the three commonly prescribed drugs, i.e. nitrofurantoin, fluoroquinolones and co-trimoxazole for UTI in our hospital. Moreover, the data would also help the authorities to formulate antibiotic prescription guidelines especially with regards to empirical treatment for patients presenting with symptoms of UTI.

Objectives
1. To determine the spectrum of gram-negative bacteria causing urinary tract infection.
2. To determine the sensitivities to nitrofurantoin, fluoroquinolones and co-trimoxazole among the isolates.
3. To compare the sensitivities among different organisms among males and females and in outpatients and inpatients.

MATERIALS AND METHODS

Inpatient and outpatient urine samples were collected and analysed at the authors’ institution, which is a tertiary care centre. The isolates were further identified biochemically to the species level.\(^6,7\)

Antimicrobial susceptibility of isolates was done by Kirby Bauer disk diffusion method with commercially available discs (HiMedia) on Mueller-Hinton agar plates according to the CLSI standards.\(^8\)

We retrospectively studied the susceptibility patterns of gram-negative isolates for 2 yrs. from October 2014 to September 2016 to nitrofurantoin, fluoroquinolones and co-trimoxazole. The results were analysed statistically by χ² test.

RESULTS

A total of 484 isolates from urine were gram-negative bacilli. Out of these, 300 were E. coli, 138 were other Enterobacteriaceae (Klebsiella- 114, Enterobacter- 8, Citrobacter- 8, Proteus- 7, Providencia- 1), 46 were non-fermenters (Acinetobacter spp.- 30 and Pseudomonas- 16). Proteus spp. were not included in the data analysis since it is intrinsically resistant to nitrofurantoin. The isolates which showed intermediate susceptibility were included along with the susceptible isolates since all the antibiotics used in the study are concentrated in the urine and hence they would be clinically susceptible.

Out of the 477 isolates, 135 were from outpatients, 304 were from inpatients admitted to wards and 38 were from inpatients admitted to the Intensive Care Units (NICU, SICU, CCU and MICU). Majority of the isolates was from female patients (340/477).

Among the 477 isolates, 82.6% were sensitive to nitrofurantoin, 56.6% were sensitive to fluoroquinolones and 43.6% were sensitive to co-trimoxazole. E. coli isolates showed 92% susceptibility to nitrofurantoin, 52% to fluoroquinolones and 41% susceptibility to co-trimoxazole. Other Enterobacteriaceae (excluding Proteus) showed lower sensitivity rates to nitrofurantoin (81.7%), but slightly higher susceptibility rates to fluoroquinolones (67.9%) and co-trimoxazole (51.1%). The non-fermenters demonstrated a much lower sensitivity rates to nitrofurantoin (23.9%). The susceptibility to fluoroquinolones and co-trimoxazole were relatively higher as per Table 1.

<table>
<thead>
<tr>
<th>Organism</th>
<th>Nitrofurantoin No. (%)</th>
<th>Fluoroquinolones No. (%)</th>
<th>Co-Tri-moxazole No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli (300)</td>
<td>276 (92)</td>
<td>156 (52)</td>
<td>123 (41)</td>
</tr>
<tr>
<td>Other Enterobacteriaceae (131)</td>
<td>107 (81.7)</td>
<td>89 (67.9)</td>
<td>67 (51.1)</td>
</tr>
<tr>
<td>Non-fermenters (46)</td>
<td>11 (23.9)</td>
<td>25 (54.4)</td>
<td>18 (39.1)</td>
</tr>
<tr>
<td><strong>Total (477)</strong></td>
<td><strong>394 (82.6)</strong></td>
<td><strong>270 (56.6)</strong></td>
<td><strong>208 (43.6)</strong></td>
</tr>
</tbody>
</table>

**Table 1. Sensitivity Rates of Different Organisms to Nitrofurantoin, Fluoroquinolones and Co-Tri-Moxazole**

Among E. coli 53.7% and among Klebsiella 48.2% were ESBL producers. Both ESBL positive and negative isolates showed high level of sensitivity to nitrofurantoin as per Table 2.

<table>
<thead>
<tr>
<th>Isolates</th>
<th>Nitrofurantoin No. (%)</th>
<th>Fluoroquinolones No. (%)</th>
<th>Co-Tri-Moxazole No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESBL positive</td>
<td>183 (84.7)</td>
<td>62 (28.7)</td>
<td>44 (20.4)</td>
</tr>
<tr>
<td>ESBL negative</td>
<td>186 (94)</td>
<td>168 (84.8)</td>
<td>138 (69.7)</td>
</tr>
</tbody>
</table>

**Table 2. Sensitivity Rates of ESBL Positive Isolates and ESBL Negative Isolates to Nitrofurantoin, Fluoroquinolones and Co-Tri-Moxazole**

Among the isolates from outpatients, 91.1% were sensitive to nitrofurantoin, 81.6% were sensitive among inpatients admitted to wards and 60.5% were sensitive among inpatients admitted in the ICUs. Sensitivity to fluoroquinolones was much lesser- outpatients 80%, inpatients 48.7% and ICU patients 36.8%. The sensitivity to co-trimoxazole among outpatients was 58.5%; among inpatients, it was 38.8%; and in ICU patients, it was 28.9% (refer to Table 3).

Sensitivity rate to nitrofurantoin was 78.1% among the males and 84.4% among the females. Slightly higher rates of sensitivities to fluoroquinolones and co-trimoxazole were observed in females as shown in Table 4.

Table 3. Susceptibility Pattern of Isolates from Outpatients, Inpatients Admitted to Wards and Inpatients Admitted to ICU to Nitrofurantoin, Fluoroquinolones and Co-Trimoxazole

<table>
<thead>
<tr>
<th></th>
<th>Nitrofurantoin No. (%)</th>
<th>Fluoroquinolones No. (%)</th>
<th>Co-Trimoxazole No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OP (135)</td>
<td>123 (91.1)</td>
<td>108 (80)</td>
<td>79 (58.5)</td>
</tr>
<tr>
<td>IP-Wards (304)</td>
<td>248 (81.6)</td>
<td>148 (48.7)</td>
<td>118 (38.8)</td>
</tr>
<tr>
<td>IP-ICU (38)</td>
<td>23 (60.5)</td>
<td>14 (36.8)</td>
<td>11 (28.9)</td>
</tr>
</tbody>
</table>

Table 4. Sensitivity Rates of Isolates from Males and Females to Nitrofurantoin, Fluoroquinolones and Co-Trimoxazole

<table>
<thead>
<tr>
<th></th>
<th>Nitrofurantoin No. (%)</th>
<th>Fluoroquinolones No. (%)</th>
<th>Co-Trimoxazole No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males (137)</td>
<td>107 (78.1)</td>
<td>59 (43.1)</td>
<td>44 (32.1)</td>
</tr>
<tr>
<td>Females (340)</td>
<td>287 (84.4)</td>
<td>211 (62)</td>
<td>164 (48.2)</td>
</tr>
</tbody>
</table>

Table 5. Sensitivity Rates of Isolates from Various Age Groups to Nitrofurantoin, Fluoroquinolones and Co-Trimoxazole

<table>
<thead>
<tr>
<th></th>
<th>Nitrofurantoin No. (%)</th>
<th>Fluoroquinolones No. (%)</th>
<th>Co-Trimoxazole No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-15 (89)</td>
<td>77 (86.5)</td>
<td>56 (62.9)</td>
<td>30 (33.7)</td>
</tr>
<tr>
<td>15-45 (243)</td>
<td>208 (85.6)</td>
<td>159 (65.4)</td>
<td>134 (55.1)</td>
</tr>
<tr>
<td>&gt;45 (145)</td>
<td>109 (75.2)</td>
<td>55 (37.9)</td>
<td>42 (29)</td>
</tr>
</tbody>
</table>

The difference in susceptibility to nitrofurantoin was statistically highly significant among the outpatients and inpatients (p <0.01) and among various organisms (p <0.01). There was no statistically significant difference between the sexes (p >0.05) and among various age groups (p >0.05). The difference in susceptibility between nitrofurantoin, fluoroquinolones and co-trimoxazole was statistically significant among the isolates from inpatients admitted to the wards and ICU (p <0.01) and among different organisms (p <0.01). The difference in susceptibility between the antibiotics was statistically significant also among the sexes (p <0.01) and among various age groups (p <0.01).

DISCUSSION

Most commonly isolated organism in our study was E. coli. The spectrum of bacterial species isolated was similar to those described in several previous studies.

In the present study, overall sensitivity among the gram-negative bacilli to nitrofurantoin was 82.6%, whereas it was 51.6% to fluoroquinolones and 42.3% to co-trimoxazole. In this study, E. coli showed 92% sensitive rate to nitrofurantoin, 52% to fluoroquinolones and 41% to co-trimoxazole. Other Enterobacteriaceae exhibited the following sensitivity rates - 81.7% to nitrofurantoin, 67.9% to fluoroquinolones and 51.1% to co-trimoxazole. The non-fermenters showed higher level of sensitivity to fluoroquinolones (54.4%) than to nitrofurantoin (23.9%) and co-trimoxazole (39.1%).

Before 1990, resistance to co-trimoxazole was 0%-5%. By the early-to-mid 1990s, studies were reporting that 7%-18% of E. coli strains causing cystitis were resistant to co-trimoxazole and a rise in resistance to fluoroquinolones was also observed.

Studies have shown that nitrofurantoin was the most active agent against uropathogens and higher rates of resistance was observed for co-trimoxazole and fluoroquinolones. A study by Kashanian et al, which studied E. coli urine isolates from 2003 to 2007 showed that 95.6% were susceptible to nitrofurantoin. By contrast, E. coli uropathogens had a mean 76% susceptibility rate to fluoroquinolones. Co-trimoxazole had a mean 29% resistance rate to E. coli in the same study. The results of the NAUTICA study by Zhanel et al showed that 21.3% of their E. coli isolates were resistant to co-trimoxazole, 5.5% to fluoroquinolones and 1.1% to nitrofurantoin.

Studies in Indian subcontinent have demonstrated slightly lower sensitivity rates. A multicentric study in India by Kothari and Sagar demonstrated that 35.8% of all gram-negative bacilli were sensitive to fluoroquinolones; 30% to co-trimoxazole; 65.7% to nitrofurantoin. Among the E. coli isolates, sensitivity to nitrofurantoin (75.6%) was relatively much higher than that to fluoroquinolones (28%) and co-trimoxazole (26%). Similar results were observed by Tankhivale et al, 62.5% sensitive to nitrofurantoin, 44.9% to fluoroquinolones and 18% to co-trimoxazole. The results of the present study are similar to these studies.

Data presented in this study indicate that antibiotics commonly used in UTI like fluoroquinolones and co-trimoxazole are showing reduced susceptibility. The present study showed better sensitivity rates for nitrofurantoin both among the isolates from outpatient setting as well as inpatient setting. Several studies have shown that nitrofurantoin has retained a high prevalence of sensitivity to most uropathogens and has a favourable side-effect profile and is cost effective.
CONCLUSION
The worldwide trend of empirically treating community acquired UTI may not apply for specific geographical regions such as India where decreased susceptibility rates are documented for common urinary pathogens. Development of specific guidelines based on local susceptibility patterns and regular surveillance is necessary for optimal empirical therapy for patients with UTI. We consider that nitrofurantoin is an acceptable empirical treatment for uncomplicated UTI particularly in the outpatient setup. Empirical treatment for nosocomial UTI or infection with multi-drug resistant isolates remains a challenge. Followup prospective randomised trials are needed to identify the exact cure rates of UTI with nitrofurantoin and other antibiotics.

REFERENCES