NITROFURANTOIN: THE TIME-TESTED CHOICE IN UNCOMPLICATED URINARY TRACT INFECTION

Jayashree Konar1, Ranadeep Ghosh2, Shiv Sekhar Chatterjee3, Amit Kumar Majumdar4, Mrinmoy Pathak5, Susmita Bhattacharya6

1Demonstrator, Department of Microbiology, NRS Medical College, Kolkata.
2Assistant Professor, Department of Microbiology, NRS Medical College, Kolkata.
3Assistant Professor, Department of Microbiology, NRS Medical College, Kolkata.
4Assistant Professor, Department of Microbiology, NRS Medical College, Kolkata.
5Demonstrator, Department of Microbiology, NRS Medical College, Kolkata.
6Professor, Department of Microbiology, NRS Medical College, Kolkata.

DOI: 10.14260/jemds/2016/442

ABSTRACT

Uropathogenic Escherichia Coli (UPEC) is the leading pathogen that causes community acquired as well as nosocomial uncomplicated urinary tract infection throughout the world. The study was conducted for one year with 2557 clinically suspected cases, both In-patients and Out-patients, to find out the most common pathogenic bacteria to cause uncomplicated urinary tract infection in a tertiary care hospital, also to determine the sensitivity pattern of the leading uropathogens against commonly prescribed antimicrobials in uncomplicated urinary tract infection. Significant bacteriuria was found in 811 cases (31.71%) in this study. Amongst them, Escherichia coli was isolated in 335 (41.3%) cases and female patients outnumbered the male patients (195, i.e. 58%). Enterococcus spp. (110, i.e. 13.56%) heads the list of Gram positive uropathogens (155 cases, i.e. 19.11%). Candida spp. was isolated in 6.16% of total culture positive cases. Most of the isolated Escherichia coli were sensitive to nitrofurantoin (290, i.e. 87%). Majority of the nitrofurantoin sensitive Escherichia coli was found to be resistant to other broad spectrum antimicrobials. Carbapenemase producers was found to be 220 (75.86%) and 255 (87.93%) were Extended Spectrum Beta Lactamase (ESBL) producers. Most (87.93%) of the Escherichia coli isolates were resistant to Fluoroquinolones. Among nitrofurantoin resistant Escherichia coli, sensitivity to carbenepens was only 33.33%. Thus Nitrofurantoin in Urinary Tract Infection may be used as an empirical drug even in the era of super bugs.

KEYWORDS

Urinary Tract Infection, Escherichia Coli, Nitrofurantoin.

INTRODUCTION

Urinary Tract Infection (UTI) is one of the most common health problems in the nosocomial as well as in the community setups. Uropathogenic Escherichia Coli (UPEC) are the leading pathogen in both community acquired and nosocomial UTI throughout the world. Uncomplicated infections occur most commonly in otherwise healthy women when uropathogenic bacteria, usually Escherichia coli, ascend from the perineum into the bladder and overcome host innate immunity. Complicated infections occur in patients with an anatomical or functional abnormality of the urinary tract. Nitrofurantoin is an age old cost effective therapeutic option for uncomplicated UTI. It is on the World Health Organization’s List of Essential Medicines, the most important medications needed in a basic health system. Nitrofurantoin has been available for the treatment of UTIs since 1953. Its current uses include the treatment of uncomplicated UTIs and prophylaxis against UTIs in people prone to recurrent UTIs. The drug works by causing damage to the bacterial DNA, since its reduced form is highly reactive. This is made possible by the rapid reduction of nitrofurantoin inside the bacterial cell by flavoproteins (Nitrofurantoin reductase) to multiple reactive intermediates that attack ribosomal proteins, DNA, enzymes involved in respiration and pyruvate metabolism within the cell.

Financial or Other, Competing Interest: None.
Submission 09-03-2016, Peer Review 04-04-2016, Acceptance 11-04-2016, Published 26-04-2016.
Corresponding Author: Dr. Susmita Bhattacharya, Professor, Department of Microbiology, Nil Ratan Sircar Medical College, 138 AJC Bose Road, Kolkata-700014. E-mail: sbhattacharya@yahoo.co.in DOI: 10.14260/jemds/2016/442

Now-a-days, there are different guidelines that emphasize on the use of Fluoroquinolones and Cotrimoxazole. Again, Carbapenems in spite of being a parenteral option, are also preferred by several schools.\textsuperscript{15,16}

Keeping these issues in mind, the present study was undertaken with a view to determine the leading uropathogen along with its antimicrobial susceptibility pattern in order to find out an effective prophylactic and therapeutic option for uncomplicated UTI.

**AIMS AND OBJECTIVES**

1. Identification of the most common pathogenic bacteria causing uncomplicated urinary tract infection in a tertiary care hospital in the last one year (2015).
2. Determine the sensitivity pattern of this leading uropathogen against commonly prescribed antimicrobials in uncomplicated urinary tract infection.

**MATERIAL AND METHODS**

The study was performed from January 2015 to December 2015 with 2557 clinically suspected patients of uncomplicated urinary tract infection. Symptomatic presence of any of the clinical symptoms of UTI like urinary urgency, hesitancy, increased frequency of micturition, pyrexia and dysuria were under the inclusion criteria. Immunocompromised patients, patients with renal transplantation and any other comorbidity were excluded from the study. Microbiological work-up to isolate and identify the bacterial pathogen was done as per standard protocol from aseptically collected urine according to standard guidelines.\textsuperscript{17} Antibiogram was done by Kirby Bauer disk diffusion technique and interpretation was done according to Clinical Laboratory Standard Institute (CLSI) guidelines.\textsuperscript{17} Data compilation and interpretation was performed as per standard statistical methods. For antibiotic susceptibility testing, drug discs of Nitrofurantoin (300 μg), Imipenem (10 μg), Meropenem (10 μg) Levofloxacin (5 μg), Ceftazidime (30 μg), Ceftazidime/clavulanic acid (30/10 μg) and Amikacin (30 μg) were used.

**Phenotypic Confirmatory Test for Detection of Extended Spectrum Beta Lactamase (Combination Disc Diffusion Test as per CLSI Guidelines).**\textsuperscript{17} Ceftazidime (30 μg) disc alone and Ceftazidime/clavulanic acid (30/10 μg) were placed at a distance of 25 mm, centre to centre, on a Mueller Hinton Agar plate inoculated with a bacterial suspension of 0.5 McFarland turbidity. Overnight incubation then done at 37°C.

If the zone of inhibition is ≥5 mm diameter for a positive test produced a clover leaf-like indentation of the bacterial strain was cultured by lawn technique on Mueller Hinton agar plate. A 10 μg meropenem disc was placed in the centre of the test area. Test organism was streaked in straight line from the edge of the disc to the edge of the plate. The plate was then incubated overnight at 37°C in ambient air. A majority (195 cases - 58%) of isolated Escherichia coli was reported from female cases (Figure 1).

Most of the isolated Escherichia coli were sensitive to nitrofurantoin (290 isolates - 87%) (Figure 2) and the rest 45 (13.43%) isolates were found to be resistant to this drug. Majority of the nitrofurantoin sensitive Escherichia coli was resistant to other broad spectrum antimicrobials. Amongst them, 220 (75.86%) were carbapenemase producers, 255 (87.93%) were Extended Spectrum Beta Lactamase (ESBL) producers and 170 (58.62%) were resistant to aminoglycoside antimicrobials. Most (87.93%) of the Escherichia coli isolates were resistant to fluoroquinolone antibiotics (Figure 3).

In 33.33% cases, uropathogenic Escherichia coli were found to be sensitive to carbapenems, although they were resistant to nitrofurantoin (Figure 4).

**RESULT**

The study was conducted for a period of one year with 2557 clinically suspected cases, both In-patients and Out-patients. A fair proportion of the patients gave the history of catheterization or instrumentation. It was found that significant number of bacteria could be isolated in 811 cases (31.71%). Amongst them Escherichia coli were isolated in 335 cases (41.3%), whereas Gram positive uropathogen was isolated in 155 cases (19.11%). Enterococcus spp. headed the list of Gram positive uropathogens - 110 cases (13.56%). Candida spp. was isolated in 6.16% (Table 1).

Majority (195 cases - 58%) of isolated Escherichia coli was reported from female cases (Figure 1).

![Fig. 1: Pie Chart showing Gender Distribution of Uropathogenic Escherichia coli (n=335)](image-url)
The study was conducted for a period of one year with 2557 clinically suspected UTI cases, both In-patients and Out-patients. A fair proportion of the patients gave history of catherization or instrumentation. It was found that significant number of bacteria could be isolated in 811 cases (31.71%). The culture negative cases may be caused by fastidious pathogens or may be because of institution of empirical antimicrobials before sample collection. Majority (195, i.e. 58%) of isolated Escherichia coli was reported from female cases. Amin et al found 553 (8.7%) patients to be urine culture positive (68% females) in their study conducted in Iran.

Amongst these 811 culture-positive cases, Escherichia coli was isolated in 335 cases (41.3%) when the total number of Gram negative pathogens was 606. The Gram positive uropathogens were isolated in 155 cases (19.11%) out of the total number of 811 culture positive cases. Enterococcus spp. headed the list of Gram positive uropathogens (110 out of 811 cases, i.e. 13.56%). Candida spp. was isolated in 50 cases, i.e. 6.16% of total culture positive cases. Study conducted by Komala et al in India showed distribution of various microbes for causing the UTI: E. coli 79%, S. saprophyticus 11%, Klebsiella 3%, Proteus spp. 2%, Enterococcus 2%, others 2%, thus E. coli being the leading uropathogen. 19

Most (290, i.e. 87%) of the isolated Escherichia coli were sensitive to nitrofurantoin. Similarly, R Nalini et al in India found that 85.19% UPEC were sensitive to nitrofurantoin and Kibret M et al from Ethiopia reported 96.4% of UPEC isolates to be sensitive to nitrofurantoin.20,21 Majority of the 290 nitrofurantoin sensitive Escherichia coli were resistant to other broad spectrum antimicrobials: 220 (75.86%) were carbapenemase producers, 255 (87.93%) were Extended Spectrum Beta Lactamase (ESBL) producers, 170 (58.62%) were resistant to aminoglycoside and 255 (87.93%) were resistant to fluoroquinolone group of antibiotics. According to the study conducted by Zhanel G et al, Mean Resistance Rates for 2,000 urinary tract isolates collected from outpatients across Canada in 1998 for ampicillin, trimethoprim-sulfamethoxazole, mecillinam, nitrofurantoin and ciprofloxacin were 41.1, 19.2, 14.7, 5.0 and 1.8%, respectively. For Escherichia coli isolates alone (n=1,681) comparable rates were 41.0, 18.9, 7.4, 0.1 and 1.2%, respectively.22 However, Goenka et al showed that among the tested antibiotics, the susceptibility of Gram negative bacteria against piperacillin-tazobactam, imipenem, amikacin and gentamicin was found to be quite high.

Several workers like Kromann-Andersen B et al, has concluded that ofloxacin is an orally active drug, which offered a valuable alternative to other broad spectrum antibacterial drugs.23 In the present study, however, nitrofurantoin resistant UPEC were found to be sensitive to ofloxacin in only 20% cases. We have found that nitrofurantoin resistant uropathogens were mostly sensitive to carbapenems (33.3%), followed by betalactam and betalactamase inhibitor combinations (26.67%). This study also revealed that these strains were least sensitive to aminoglycosides and fluoroquinolones (20% each). It may be due to in judicious use of these drugs in this particular setup.

DISCUSSION
The study was conducted for a period of one year with 2557 clinically suspected UTI cases, both In-patients and Out-patients. A fair proportion of the patients gave history of catherization or instrumentation. It was found that significant number of bacteria could be isolated in 811 cases (31.71%). The culture negative cases may be caused by fastidious pathogens or may be because of institution of empirical antimicrobials before sample collection. Majority (195, i.e. 58%) of isolated Escherichia coli was reported from female cases. Amin et al found 553 (8.7%) patients to be urine culture positive (68% females) in their study conducted in Iran. 19

Amongst these 811 culture-positive cases, Escherichia coli was isolated in 335 cases (41.3%) when the total number of Gram negative pathogens was 606. The Gram positive uropathogens were isolated in 155 cases (19.11%) out of the total number of 811 culture positive cases. Enterococcus spp. headed the list of Gram positive uropathogens (110 out of 811 cases, i.e. 13.56%). Candida spp. was isolated in 50 cases, i.e. 6.16% of total culture positive cases. Study conducted by Komala et al in India showed distribution of various microbes for causing the UTI: E. coli 79%, S. saprophyticus 11%, Klebsiella 3%, Proteus spp. 2%, Enterococcus 2%, others 2%, thus E. coli being the leading uropathogen. 19

Most (290, i.e. 87%) of the isolated Escherichia coli were sensitive to nitrofurantoin. Similarly, R Nalini et al in India found that 85.19% UPEC were sensitive to nitrofurantoin and Kibret M et al from Ethiopia reported 96.4% of UPEC isolates to be sensitive to nitrofurantoin.20,21 Majority of the 290 nitrofurantoin sensitive Escherichia coli were resistant to other broad spectrum antimicrobials: 220 (75.86%) were carbapenemase producers, 255 (87.93%) were Extended Spectrum Beta Lactamase (ESBL) producers, 170 (58.62%) were resistant to aminoglycoside and 255 (87.93%) were resistant to fluoroquinolone group of antibiotics. According to the study conducted by Zhanel G et al, Mean Resistance Rates for 2,000 urinary tract isolates collected from outpatients across Canada in 1998 for ampicillin, trimethoprim-sulfamethoxazole, mecillinam, nitrofurantoin and ciprofloxacin were 41.1, 19.2, 14.7, 5.0 and 1.8%, respectively. For Escherichia coli isolates alone (n=1,681) comparable rates were 41.0, 18.9, 7.4, 0.1 and 1.2%, respectively.22 However, Goenka et al showed that among the tested antibiotics, the susceptibility of Gram negative bacteria against piperacillin-tazobactam, imipenem, amikacin and gentamicin was found to be quite high.

Several workers like Kromann-Andersen B et al, has concluded that ofloxacin is an orally active drug, which offered a valuable alternative to other broad spectrum antibacterial drugs.23 In the present study, however, nitrofurantoin resistant UPEC were found to be sensitive to ofloxacin in only 20% cases. We have found that nitrofurantoin resistant uropathogens were mostly sensitive to carbapenems (33.3%), followed by betalactam and betalactamase inhibitor combinations (26.67%). This study also revealed that these strains were least sensitive to aminoglycosides and fluoroquinolones (20% each). It may be due to in judicious use of these drugs in this particular setup.

CONCLUSION
UTI, one of the major health problems in India especially for female, is predominantly caused by Escherichia coli. Nitrofurantoin, a safe antimicrobial drug as per literature is found to be the most effective therapeutic option for treating uncomplicated UTI even in multidrug resistant UPEC. Thus, the use of nitrofurantoin in UTI may be advocated as an empirical drug even in the era of super bugs in our institution as revealed in this current study. Similar study should be continued to institute proper empirical therapy of the patients, because of the ever changing sensitivity pattern.

LIMITATION
The mechanism of drug resistance has not been studied in this current work. The strains have been preserved for future
molecular characterization and determination of the cause of drug resistance.

ACKNOWLEDGEMENTS

We are very much grateful to the Principal, Dean - Student Affairs and Head of the Department of Microbiology, Nilratan Sircar Medical College and Hospital, Kolkata, for their kind permission and cooperation in conducting this study.

REFERENCES