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Original Article

Microbiology Section

Nitrofurantoin Revisited for Uropathogens: Easing out Therapeutic Dilemma for Clinicians in an Upcoming Super Speciality Hospital

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ABSTRACT

Introduction: Urinary Tract Infection (UTI) which is caused by antibiotic resistant uropathogens has become a major health jeopardy in recent years as it is difficult to treat, causing an increase in morbidity and mortality. Knowledge regarding the local antibiogram of the specific area would provide better treatment options for the clinicians while tackling drug resistant uropathogens.

Aim: To review the susceptibility pattern of the uropathogens isolated from the patient population referred to the super speciality hospital in the East Delhi area.

Materials and Methods: The retrospective study was conducted in the Department of Microbiology of an upcoming super speciality hospital from January 2017 to December 2017. A total of 2362 samples included clean-catch mid-stream urine, aspirates from catheter tube or suprapubic aspirate collected aseptically. Semi quantitative culture was performed by inoculating urine on Cysteine-Lactose-Electrolyte-Deficient agar (CLED) media using a calibrated nichrome loop. The plates were aerobically incubated at 37°C overnight. Pure growth of a single isolate in a count of $\geq 10^5$ Colony Forming Units (CFU) per millilitre of urine was considered as significant bacteriuria. Antimicrobial Susceptibility Tests (AST) of the isolates was done by VITEK-2 Compact (BioMerieux, France) system as per Clinical and Laboratory Standards Institute 2017 (CLSI) guidelines. Data collected was compiled and entered into Microsoft excel sheets, and percentages were used to interpret and analyse the findings.

Results: *Escherichia coli (E.coli)* was the most frequent uropathogen accounting to 155/247 (62.75%) followed by *Klebsiella* species 41/247 (16.59%) and *Pseudomonas aeruginosa* 20/247 (8.09%). Nitrofurantoin sensitivity was shown by 73/90 (81.1%) of Non-Extended Spectrum Beta Lactamase (ESBL) producing and 52/65 (80%) of ESBL producing *E. coli* isolates. Amongst *Klebsiella* species, 13/20 (65%) of Non ESBL producing and 10/21 (47.6%) of ESBL producing were sensitive to Nitrofurantoin.

Conclusion: The drug nitrofurantoin definitely fared well in the sensitivity pattern over high resistance potential antibiotics like fluoroquinolones in the present study. In an era of antibiotic overtreatment and fostering resistant bugs; bringing out local antibiogram would ease out the therapeutic dilemma for clinicians and assuredly avert the antibiotic menace.

Keywords: *Escherichia coli*, Extended spectrum beta lactamase, *Klebsiella pneumoniae*, Urinary tract infection

INTRODUCTION

The upsurge of drug resistant uropathogens in recent years has perplexed the treatment of Urinary Tract Infections (UTIs), causing an escalation in morbidity and mortality. *E.coli* is the most common bug responsible for more than 80% of UTIs while *Klebsiella pneumoniae*, *Proteus mirabilis*, *Staphylococcus aureus*, *Enterococcus* species and *Pseudomonas aeruginosa* are more to be reeled off in the list of causative agents [1].

Exaltation in the incidence of antimicrobial resistance, especially Multidrug Resistant (MDR) uropathogens is well published in literature [2]. Resistance to the few novel antibiotics is also emerging and in this circumstance, the rational use of older antibiotics would represent an alternative to the treatment of MDR bacterial pathogens which would help to optimise the use of antibiotics in the way to preserve new antibiotics, thereby avoiding the spread of resistance [3].

The past decade has ratified a substantial use of fluoroquinolones and cephalosporins to treat UTIs and their subsequent resistance [4]. While literature search identifies MDR *E.coli* for community acquired UTIs globally still, Nitrofurantoin is the key player in combating resistance worldwide [5]. Nitrofurantoin is a befitting choice as it has minimum resistance, least disposition for collateral damage while efficacy comparable to trimethoprim-sulfamethoxazole [6]. To trace back, though the drug was clinically introduced in 1952 for treatment of acute uncomplicated UTIs and continued few years thereafter, its acceptance decreased in 1970s with the influx of oral antibiotics like co-trimoxazole and β-lactams. Nevertheless, the hastily increasing resistance to co-trimoxazole and fluoroquinolones has revived interest in this veteran drug [7,8].

To ease out the therapeutic dilemma for "high resistance potential antibiotics" in a tertiary care set up, the clinicians require an insight into the virtues of nitrofurantoin. This contemporary study was planned with the perspective to review the susceptibility pattern of the uropathogens isolated from the patient population referred to the super speciality hospital in the east Delhi area.

MATERIALS AND METHODS

A retrospective study was conducted in the Department of Microbiology of Rajiv Gandhi Super Speciality Hospital, an upcoming super speciality hospital from January 2017 to December 2017. Thereafter, the data was compiled by July 2018. The study included clinically suspected patients having UTI (outdoor/ambulatory patients and indoor/hospitalised patients). Those samples were considered which belonged to patients of adult age group and of non-pregnant females. Confidentiality of the patients was ensured. The data were retrieved from the laboratory register of Microbiology department.

A total of 2362 samples included clean-catch mid-stream urine, aspirates from catheter tube or suprapubic aspirate collected aseptically; were received in a sterile, wide-mouthed and screw capped container. For semi-quantitative culture which was performed by inoculating urine on Cysteine-Lactose-Electrolyte-Deficient agar (CLED) agar media, a sterile 4 mm nichrome calibrated loop which carries 0.001 mL of urine was used. The plates were aerobically

incubated at 37°C overnight. Pure growth of a single isolate in a count of ≥10^5 Colony Forming Units (CFU) per millilitre of urine was considered as significant bacteriuria.

Inclusion Criteria: Positive pure bacterial cultures of symptomatic, clinically suspected patients of UTI.

Exclusion Criteria: The isolates identified as contaminant or same isolates from repeated culture.

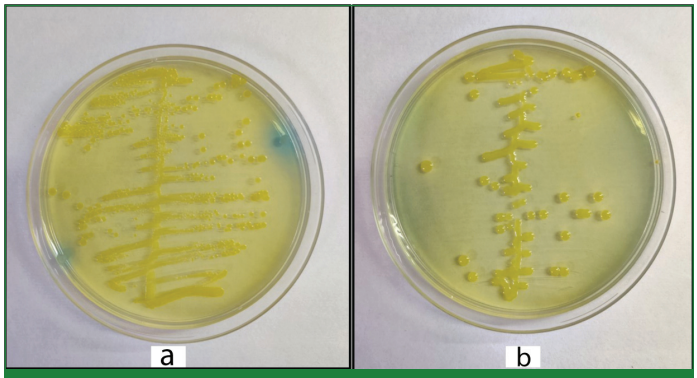
The identification and Antimicrobial Susceptibility Tests (AST) of the urinary isolates was done by VITEK-2 Compact (BioMerieux, France) system. For the identification of bacteria, Gram Negative (GN) and Gram Positive (GP) ID cards were used. AST and the minimum inhibitory concentrations were determined by AST cards for GP and GN organisms, respectively. The antibiotics tested for Gram negative microbes included ampicillin, gentamicin, amoxicillin/clavulanic acid, piperacillin/tazobactam, cefuroxime, ceftazidime, cefepime, ciprofloxacin, trimethoprim/sulfamethoxazole, imipenem and nitrofurantoin. Interpretation of AST results were as per the Advanced Expert System of the VITEK-2 Compact (BioMerieux, France) system. Extended Spectrum Beta Lactamase (ESBL) detection of isolates was verified by the Clinical and Laboratory Standards Institute (CLSI) 2017 guidelines [9]; based on analysis of Minimum Inhibitory Concentration (MIC) patterns with the Advanced Expert System.

STATISTICAL ANALYSIS

Analysis was done by compiling all the data and entered into Microsoft excel sheets, and doubly checked for any key board error. Findings was analysed and interpret in percentages.

RESULTS

In the retrospective laboratory-based study, 2362 urine samples were obtained during the study period. Significant bacterial growth was seen in 247 urinary samples as shown in [Table/Fig-1]. Gender wise analysis of positive urinary culture showed 143 (57.9%) samples were from males and 104 (42.1%) from females. The mean age of males and females was 52.3±1.15 years and 47.4±1.15 years, respectively.



[Table/Fig-1]: Figure showing significant bacterial growth (≥10^5 CFU/ml) of: (a) *Escherichia coli*: and (b) *Klebsiella pneumoniae.*

The most common Gram negative uropathogen was *Escherichia coli* 155/247 (62.75%) followed by *Klebsiella pneumoniae* 41/247 (16.59%), *Pseudomonas aeruginosa* 20/247 (8.09%), and others members of Enterobacteriaceae. Gram Positive uropathogens were *Enterococcus* species 11/247 (4.45%) and *Staphylococcus aureus* 3/247 (1.21%) as shown in [Table/Fig-2]. Amongst all the uropathogens isolated, *E. coli* shows maximum susceptibility towards Nitrofurantoin (80%).

Detection of ESBL producing uropathogens was seen in 65/155 (41.9 %) of *E. coli* and 21/41 (51.2%) of *K. pneumoniae* isolates. Comparison of Non-ESBL and ESBL producing *E. coli* shows 81.11% and 80% sensitivity respectively towards Nitrofurantoin while it is 65% and 47.61% for *K. pneumoniae* isolates as delineated in [Table/Fig-3].

Antibiogram of major uropathogens, *E. coli* and *K.pneumoniae* were analysed. *E.coli* shows maximum susceptibility to carbapenems (Imipenem 83.87%), least to cefuroxime (0.6%) and so does *K. Pneumoniae* (87.8% and 2.4%, respectively). The susceptibility to fluoroquinolones (ciprofloxacin) is 18.7% in *E.coli* and 34.14% in *Klebsiella pneumoniae* as shown in [Table/Fig-4].

Micro-organism	No. of isolates (%)	Nitrofurantoin sensitivity (%)
Gram negative uropathogens		
Escherichia coli	155 (62.75%)	125 (80%)
Klebsiella pneumoniae	41 (16.59%)	23 (56%)
Enterobacter species	3 (1.21%)	2 (66%)
Pantoea species	1 (0.4%)	0 (0%)
Gram Positive uropathogens		
Enterococcus species	11 (4.45%)	7 (63%)
Staphylococcus aureus	3 (1.21%)	2 (66.67%)
Staphylococcus saprophyticus	1 (0.4%)	1 (100%)

[Table/Fig-2]: Sensitivity of uropathogens to Nitrofurantoin.
* *Pseudomonas aeruginosa* 20 (8.09%), isolates of Proteae tribe (*Proteus* species, *Morganella morganii*, *Providencia* species) 10 (4.04%) and *Serratia* species 2(0.8%) show inherent resistance; {Out of n=247, only 215 isolates tested for Nitrofurantoin (*32 isolates showed inherent resistance)}

Antibiotic	*E.coli* (155)		*Klebsiella pneumoniae* (41)	
	Non ESBL producers n=90 (% Sensitive)	ESBL producers n=65 (% Sensitive)	Non ESBL producers n=20 (%Sensitive)	ESBL Producers n=21 (% Sensitive)
Nitrofurantoin sensitive (%)	73 (81.11%)	52 (80%)	13 (65%)	10 (47.61%)

[Table/Fig-3]: Nitrofurantoin sensitivity in ESBL and Non-ESBL *E. coli* and *K. pneumoniae*.

Antibiotics	No. of isolates sensitive to antibiotics (%)	
	Escherichia coli (n=155)	*Klebsiella. pneumoniae* (n=41)
Ampicillin	13 (8.3%)	2 (4.8%)
Gentamicin	83 (53.54%)	25 (60.97%)
Amikacin	43 (27.7%)	17 (41.4%)
Amoxicillin/Clavulanic acid	56 (36.12%)	20 (48.7%)
Piperacillin/Tazobactum	105 (67.74%)	24 (58.53%)
Cefuroxime	1 (0.6%)	1 (2.4%)
Ceftazidime	22 (14.19%)	6 (14.63%)
Cefepime	27 (17.41%)	6 (14.63%)
Ciprofloxacin	29 (18.7%)	14 (34.14%)
Co-trimoxazole	61 (39.35%)	22 (53.6%)
Nitrofurantoin	125 (80.6%)	23 (56.09%)
Imipenem	130 (83.87%)	36 (87.8%)

[Table/Fig-4]: Antibiogram of *Escherichia coli* and *Klebsiella pneumoniae* isolates showing sensitivity pattern to various tested antibiotics.

DISCUSSION

Optimal therapy for UTI in today's clinical setting of impending post antibiotic era depends on the severity of illness at presentation, resistance patterns available through continuous, unbiased surveillance of antibiotic susceptibility motifs of uropathogens at local level as well as specific host factors. Urine culture and its AST should be performed, and initial empirical therapy should be modified appropriately on the basis of the infecting uropathogens [6]. The current study focussed for better understanding of uropathogens in the east Delhi area and subduing antimicrobial decisions for clinicians by revisiting Nitrofurantoin.

A total of 247 positive urine cultures during one-year period (January-December 2017) were analysed in this study. Gender-wise, males 143/247 (57.9%) were more affected than females 104/247 (42.1%) in the present study; a credible rationale could

be prostate enlargement, neurogenic bladder and requirement of catheterisation in the form of intervention in males [6]. This is contradicting to the study by Gupta P and Gupta K where 52.5% were females [10]. Women are prone to conditions such as vaginitis, atrophy and prolapse of vagina which set up the path for UTI [11].

Escherichia coli, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Enterococcus* species were the main isolates of the study, the former two being the most common, similar to study done by Sood S and Gupta R [12]. *E. coli* (62.75%) was the predominant pathogen isolated incessantly from patients with symptomatic UTI in this study. A coherent finding of *E. coli* being the most common uropathogen from patients with UTIs has been reported by Kothari A and Sagar V (68%) as well [13].

CLSI guidelines recommend either disk diffusion method or broth microdilution method for detection of ESBL isolates. Automated susceptibility testing systems like VITEK with test for detection of ESBL production aids in epidemiological and infection control practices. In this study, ESBL analysis of the 196 culture positive samples showed 65/155 (42%) as ESBL producing *E. coli* and 90/155 (58%) as non ESBL producing *E. coli* which was in accordance with the study of Niranjan V and Malini A and Bency JAT et al., [14,15]. Amongst *K. pneumoniae* isolates, 21/41 (51%) were ESBL producing isolates and 20/41 (48.7%) were non ESBL producing isolates which is similar to the study done by Aggarwal R et al., [16].

Antibiotic sensitivity pattern of *E.coli* and *K. pneumoniae* was observed in the present study of which 80% of *E.coli* isolates were sensitive to Nitrofurantoin and among that ESBL positive *E. coli* was 80% sensitive to Nitrofurantoin which is in accordance with the study conducted by Rajendran V et al., [17]. In this study ESBL producing *K. pneumoniae* showing sensitivity to Nitrofurantoin was 47.61% compared to non-ESBL producers which was 65% sensitive an observation similar to that reported by Procop GW et al., while in study conducted by Subathra N and Radhika R, ESBL producing *K. pneumoniae* showed 90% sensitivity to Nitrofurantoin [18,19].

Nitrofurantoin is an effective antibiotic for the treatment of uncomplicated UTIs which also contributes to overall reduction in the use of fluoroquinolones and beta-lactams. In order to use antibiotic as an agent for empiric therapy for treatment of UTIs, it should fulfil certain criteria such as: have low resistance rates against potential pathogens, ablility to achieve significant urinary concentration and must be cost effective with minimal adverse effects [6], and Nitrofurantoin is a cost-effective oral antibiotic with minimal adverse drug effects thus having good patient compliance rates.

Limitation(s)

This study was an observational one with defining data of a super speciality hospital so the results could not be implied to general health care facilities.

CONCLUSION(S)

The drug nitrofurantoin definitely fared well in the sensitivity pattern over high resistance potential antibiotics like fluoroquinolones and beta lactams amongst commonly isolated uropathogens in the present study. Diagnostic challenges faced by the clinicians while treating MDR uropathogens could be eased off optimally by the local antibiogram of the hospital. In the present scenario, antibiogram evaluation of nitrofurantoin clearly accentuates its integrity; as if customised for patient use in conjunction with combatting antibiotic misuse.

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