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Original Research Article

RESURGENCE OF NITROFURANTOIN AND FOSFOMYCIN AS EFFECTIVE ORAL EMPIRICAL TREATMENT OPTIONS FOR MULTIDRUG RESISTANT UROPATHOGENS

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Abstract

Background: Therapeutic options for the treatment of UTIs are becoming limited in an era of emerging drug resistance. Fosfomycin and nitrofurantoin are increasingly being prescribed since guidelines began recommending them as first-line therapies for lower urinary tract infections (UTI). In this study, the sensitivity profiles of uropathogens to fosfomycin and nitrofurantoin were investigated. **Materials and Methods:** Clean voided midstream urine samples from patients ≥ 16 years of age of both genders with suspected signs and symptoms of UTI were collected and was inoculated onto cysteine lactose electrolyte-deficient agar. A bacterial count of ≥105 colony forming units (CFU)/mL of urine is considered as significant and indicates infection. Antibiotic sensitivity testing was done by Kirby-Bauer disc diffusion method according to CLSI guidelines 2023. Furthermore, Fosfomycin trometamol resistance was also determined by the agar dilution method as per the CLSI guidelines 2023. **Result:** A total of 1832 urine samples were referred for culture during the study period, which yielded 385 significant bacterial isolates. The in vitro susceptibility rate of uropathogens to fosfomycin and nitrofurantoin were 96.6% and 89%, respectively. **Conclusion:** The isolated uropathogens, including MDR isolates, show high in vitro susceptibility to fosfomycin and nitrofurantoin and therefore have the potential to emerge as promising alternative oral agents for therapy of uncomplicated UTIs.

INTRODUCTION

Urinary tract infections (UTIs) are among the most common bacterial infections that need medical care. An estimated 50% of women report to have at least one episode of UTI at some point in their lives.[1] The presence of a significant amount of bacteria in urine may lead to asymptomatic bacteriuria (ABU) or indicate urinary tract Infections (UTIs), including uncomplicated and complicated UTIs. UTIs may affect only the lower urinary tract and can occur as cystitis (bladder infection), causing frequent urination, pain lower abdomen and a feeling of pressure or burning micturation. When UTIs affect the upper urinary tract, such as the ureters and kidneys, they may also cause fever, vomiting, back pain and even hematuria. Rarely, UTIs can lead to renal failure or urosepsis and can be life-threatening.[1] Empirical therapy for urinary tract infection (UTI) is based on the susceptibility patterns of locally isolated bacteria in a given time period.[1,2] Uncomplicated urinary tract infections (UTIs) are treated with beta-lactams, co-trimoxazole, quinolones, fosfomycin tromethamine and nitrofurantoin. Currently antibiotic resistance among uropathogens is a worldwide problem. Trimethoprim-sulfamethoxazole has retained clinical efficacy, but resistance rates are increasing globally. Beta-lactam antibiotics have the highest rates of resistance and lowest rates of clinical success. Among MDR uropathogens, fluoroquinolones have high resistance rates and are being strongly discouraged as first-line agents for treating UTIs.[3] Nitrofurantoin and fosfomycin are old antibiotics. They share several important properties, including high concentrations in the urinary tract, a minimal impact on gastrointestinal flora and a low propensity for resistance.[4] The FDA approved nitrofurantoin in 1953 for the treatment of lower urinary tract infections. Nitrofurantoin is a synthetic antimicrobial created from furan and an added nitro group and a side change containing hydantoin.[5] Conventional

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antibiotic therapy for acute UTIs includes trimethoprim-sulfamethoxazole, Cefpodoxime, Cephalexin and Cefuroxime, Levofloxacin, Ciprofloxacin, Cefepime, Ampicillin and Imipenem/Cilastatin. The emergence of antibiotic-resistant strains and elimination of the microbial flora of the gastrointestinal tract and vagina may occur following long-term use of these conventional antibiotics in patients suffering from UTI. Nitrofurantoin provides good empirical cover of uropathogens, reaches high concentrations in the bladder and has a low impact on endogenous resident microflora. The use of Nitrofurantoin has increased exponentially since new guidelines have repositioned it as first-line therapy for uncomplicated lower urinary tract infection (UTI).[6] In terms of urinary tract infections, 93-99% of fosfomycin is excreted unaltered in urine and barely binds to plasma proteins, disseminating widely in the renal parenchyma, bladder and uninflamed prostate.[7] Fosfomycin is recommended for cystitis in immunocompetent patients, according to the guidelines of the Infectious Diseases Society of America,[8] even in conditions with ESBL, as are nitrofurantoin and cotrimoxazole.[9] Based on the available literature, fosfomycin and nitrofurantoin should be considered highly effective alternatives for the treatment of MDR UTIs.[3,4,10]

MATERIALS AND METHODS

This study was conducted from November 2023 to April 2024 at Darbhanga Medical College Laheriasarai, Darbhanga Bihar, India, a tertiary care referral hospital.

Clean voided midstream urine specimens were collected in sterile containers and transported within 2 hours to the Department of Microbiology, Darbhanga Medical College and Hospital, Laheriasarai Darbhanga Bihar India. Culture and sensitivity testing of urine specimens were done according to standard laboratory methods.[11] Clean voided midstream urine samples were collected from patients ≥ 16 years of age of both genders with suspected signs and symptoms, along with a clinical diagnosis of lower UTI. Urine samples were inoculated onto cysteine lactose electrolyte-deficient (CLED) agar by the standard loop method and incubated overnight at 37°C. Urinary pathogens were identified as per the standard laboratory protocol by conventional biochemical tests.[11]

According to Kass concept of significant bacteriuria, uropathogen was defined as an organism known to be associated with signs and symptoms of UTI with > 105 colony forming units/mL of urine.

Urine samples from paediatric patients, patients on indwelling catheter, patients on antibiotics and patient with a suspected upper UTI (pyelonephritis) or genital or sexually transmitted infection (e.g., vaginal discharge) were excluded. If a urine specimen grew >2 organisms, it was considered contaminated and was excluded from the study.

Antimicrobial susceptibility testing was determined by the Kirby-Bauer disc diffusion method and the results were interpreted as per the guidelines of the Clinical and Laboratory Standards Institute (CLSI) 2023.[12] The following antibiotic discs were used: ampicillin 10µg, amoxicillin-clavulanate 20/10 µg, piperacillin-tazobactam 100/10 µg, cefazolin 30 µg, ceftazidime 30 µg, cefoxitin 30 µg , ciprofloxacin 5µg, levofloxacin 5µg, gentamicin 10 µg, amikacin 30 µg, (/disc), trimethoprim- sulfamethoxazole (co-trimoxazole) 1.25/23.75 µg, fosfomycin 200 µg and nitrofurantoin 300 µg. The resistance to Fosfomycin trometamol was determined by the agar dilution method as per the CLSI guidelines 2023.[12]

RESULTS

Among the 1832 urine samples processed, organisms were isolated from 485 samples yielding a positive culture rate or isolation rate of 26.5%.

The percentages of isolates from males and females were 33.7% and 56.3% respectively, which were not significantly different (Z–value = 0.55, P = 0.58).

The most commonly isolated uropathogen was Esherichia coli with 338 isolates (70%), followed by Klebsiella spp. (10%), Enterococcus spp. (5.6%), Pseudomonas spp. (3.5%), Citrobacter spp. and Staphylococcus spp. both 2.7%, Acinetobacter spp. (02%), Proteus spp. (01%) and Morganella morganii (0.4%). Proteus spp. (01%) and Morganella morganii (0.4%) were very few in numbers, so they were excluded from calculations. [Table 1].

Escherichia coli, Klebsiella spp., Enterococcus spp. and Pseudomonas spp. were the predominant isolates in our study. Isolates such as Acinetobacter spp. and Pseudomonas spp. Were predominantly isolated from indoor bedridden patients. E. coli was most susceptible to fosfomycin (97%) followed by nitrofurantoin (89%) and amikacin (84%). E. coli had the least susceptibility to cefazolin (12.7%) and ampicillin (16.6%). Klebsiella strains also exhibit similar antibiotic resistance patterns. It was most susceptible to fosfomycin (96%) followed by nitrofurantoin (83.7%) and amikacin (83%). Klebsiella spp. were least susceptible to cefazolin (22.5%) and ampicillin (22.5%). Pseudomonas spp. were most susceptible to amikacin (76.5%) followed by piperacillin-tazobactam (64.7%). Pseudomonas spp. were least susceptible to ciprofloxacin (13.5%). In our study, Enterococcus spp. were most susceptible to fosfomycin (94.3%) followed by nitrofurantoin (89%), and were least susceptible to ampicillin (14.8%). Citrobacter spp. and Enterobacter spp. also exhibited excellent sensitivity to fosfomycin followed by nitrofurantoin and amikacin.

Pathogen-wise antimicrobial resistance patterns are shown in [Table 2 and 3].

The overall susceptibility rates of uropathogens to fosfomycin, amikacin, nitrofurantoin and Piperacillin-tazobactam were 96.6%, 89%, 84% and

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80% respectively. Intermediate antibiotic sensitivity was considered as a resistant for analysis.

Table 1:

Uropathogens (Total= 485)	Number & Percentage
Escherichia coli	338 (70%)
Klebsiella spp.	49 (10%)
Enterobacter spp.	11 (2.3%)
Citrobacter spp.	13 (2.7%)
Proteus spp.	05 (01%)
Morganella morganii	02 (0.4%)
Pseudomonas spp.	17 (3.5%)
Acinetobacter spp.	10 (02%)
Enterococcus spp.	27 (5.6%)
Staphylococcus spp.	13 (2.7%)

Table 2

Antibiotics	Escherichia coli N= 338	Klebsiella spp. N= 49	Enterobacter spp. N= 11	Citrobacter spp. N= 13
Ampicillin	282 (83.4%)	38 (77.5%)	09 (82%)	10 (77%)
Cefazolin	295 (87.3%)	40 (81.6%)	09 (82%)	11 (84.6%)
Ceftazidime	178 (52.6%)	26 (53%)	06 (54.5%)	06 (46%)
Amoxicillin- clavulanic acid	193 (57%)	27 (55%)	05 (45.5%)	07 (54%)
Ciprofloxacin	227 (67.2%)	32 (65%)	08 (73%)	09 (69%)
Levofloxacin	216 (64%)	29 (59%)	07 (64%)	10 (61.5%)
Gentamicin	208 (61.5%)	31 (63%)	07 (63.6%)	09 (69.2%)
Amikacin	54 (16%)	06 (13%)	02 (18 %)	03 (23%)
Trimethoprim- sulfamethoxazole	209 (62%)	28 (57%)	06 (54.5%)	08 (61.5%)
Piperacillin- tazobactam	64 (19%)	09 (18.4%)	02 (18 %)	03 (23%)
Nitrofurantoin	37 (11%)	06 (12.2%)	01 (09%)	02 (15.4%)
Fosfomycin	11 (03%)	02 (04%)	0	01 (07.7%)

Table 3

	Pseudomonas spp. N= 17	Acinetobacter spp. N= 10	Enterococcus spp. N= 27	Staphylococcus spp. N= 13
Ampicillin			24 (85.2)	
Ceftazidime	10 (59%)	06 (60%)		
Cefoxitin				08 (61.5%)
Piperacillin- tazobactam	06 (35.3%)	04 (40%)		
Ciprofloxacin	13 (76.5%)	08 (80%)	21 (77.8%)	09 (69.2%)
Levofloxacin	11 (64.7%)	07 (70%)	17 (63%)	08 (61.5%)
Gentamicin	11 (64.7%)	07 (70%)		09 (69.2%)
Amikacin	04 (23.5%)	03 (30%)		
Trimethoprim- sulfamethoxazole		06 (60%)	17 (63%)	09 (69.2%)
Nitrofurantoin			03 (11%)	02 (15.4%)
Fosfomycin			01 (3.7%)	

Table 4: Overall percentage of resistance to common antibiotics among uropathogens

Antibiotics	Resistance rate%
Ampicillin	83% (363/438)
Cefazolin	86% (355/411)
Cefoxitin	61% (08/13)
Ceftazidime	53% (232/438)
Piperacillin- tazobactam	20% (88/438)
Amoxicillin-clavulanic acid	56% (232/411)
Ciprofloxacin	68% (327/478)
Levofloxacin	64% (305/478)
Trimethoprim-sulfamethoxazole	61% (283/461)
Gentamicin	60% (273/451)
Amikacin	16% (72/438)
Nitrofurantoin	11% (51/451)
Fosfomycin	3.4% (15/438)

DISCUSSION

Urinary tract infection (UTI) is one of the most commonly seen bacterial infections in general practice, and the proportion of prescriptions for UTI that are identified as appropriate is higher than for other bacterial infections. Most UTIs are caused by E. coli.[13-15] The most common gram-negative bacteria isolated from the samples in our investigation was E. coli (70%). These findings are consistent with those of several other published

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studies in which the prevalence of E. coli ranged from 40% to 97%.[13-16]

The positive culture rate or isolation rate of 26.5% obtained in this study was close to that obtained by similar studies conducted across India and neighboring countries.[17,18] The data obtained from this study show that the spectrum of organisms causing UTIs is also similar to that reported by other studies across India. However, the isolation rates of various organisms vary from study to study.[17-20]

In our study, E. coli was the most common isolated organism responsible for causing UTIs, which is in concordance with the findings of other studies across India.[13,14,18] The highest resistance rate was observed for cefazolin (86%) followed by ampicillin (83%). In contrast, the lowest resistance rate was observed for fosfomycin and nitrofurantoin, the recommended current first-line treatment for uncomplicated UTIs, which was similar to that observed in other studies across India.[14-18] Although amikacin has a low resistance rate, it can be used only intravenously. The susceptibility of E. coli to cotrimoxazole was 38% in our study, while in other studies across India it varied from 15.15% to 52.3%.[14,15] The susceptibility of E. coli to ciprofloxacin was 33% which was similar to the susceptibility rates reported in other studies across India and neighboring countries.[15,16,19,20]

Klebsiella spp. were the second most commonly isolated uropathogen at rate of 10%, similar to isolation rate reported in other studies from India.[14-16] The susceptibility to fosfomycin was reported to be the highest (96%) followed by that to nitrofurantoin (87.8%). Ciprofloxacin and cotrimoxazole were susceptible in 35% and 43% of the isolates respectively, as observed in other studies across India.[15,16,18]

The susceptibility of Pseudomonas isolates to the anti-pseudomonal cephalosporin ceftazidime was found 41%, while that for Piperacillin-tazobactam was 64.3%. In our study Pseudomonas spp. exhibited good sensitivity to amikacin (75.5%) as reported in other studies across India.[14,15,19]

In our study, Enterococcus spp. Were the most common gram-positive bacteria isolated from the UTI samples and third most common isolate which also in concordance with the findings of other studies.[21,22] Moreover, Enterococcus isolates were highly resistant to some antibiotics (ampicillin 85.2%, ciprofloxacin 78%, levofloxacin 63%, co-trimoxazole 63%), but were most susceptible to fosfomycin 96% and nitrofurantoin (89%) which is close to the susceptibility rates reported in various published studies.[20-23]

Overall percentage of resistance to commonly used antibiotics in uropathogens was greatest for cefazolin (86%) and ampicillin (83%), while more than 60% of uropathogens in our study exhibited resistance to ciprofloxacin, levofloxacin and trimethoprim-sulfamethoxazole, which are commonly used as empiric therapies in uncomplicated UTIs. Isolates in our study were more sensitive to fosfomycin (96.6%) followed by nitrofurantoin (89%). These findings were close to those of studies from India and neighboring countries published earlier in various publications.[15,24-27]

One of the most striking findings we found in our study was that amikacin shows excellent sensitivity with broad spectrum coverage, possessing an overall susceptibility rate of 86%, which was similar to the findings of other studies from India and neighboring countries.[15,24,28,29] Features such as intravenous use and nephrotoxicity limit it's use.

There has been an increase in the literature on the use of fosfomycin in UTIs from the western world,[30-33] but in India there are limited data on the use of fosfomycin. In the present study, the in vitro sensitivity to fosfomycin (96.6%) was consistent with that reported in other studies.[30,34,35] Nitrofurantoin has been prescribed in our setup for more than a decade, whereas fosfomycin has prescribed for the past 2 years. This may be the reason for the higher resistance rate against nitrofurantoin (sensitivity 89%) compared to fosfomycin.

National treatment guidelines for antimicrobials have recommended the use of nitrofurantoin, cotrimoxazole, and fluoroquinolone as empiric therapies for lower UTIs, but in the present study more than 60% resistance was observed against cotrimoxazole and fluoroquinolone. Hence, these drugs should not be used as empirical therapies for UTIs in the study area.

Based on this study, it can be recommended that fosfomycin and nitrofurantoin be preferred over cotrimoxazole and ciprofloxacin for use as empiric antibiotics for uncomplicated UTIs.[36,37]

CONCLUSION

This study provides important data for monitoring and comparison with other studies on the trend of antimicrobial susceptibility to uropathogens and helps us to determine the optimal treatment for UTIs at this referral healthcare center. Fosfomycin and nitrofurantoin showed good in vitro activity against uropathogens from lower UTIs and can be used for empirical therapy in our area. Similar studies should be performed on a larger scale periodically in different regions so that empiric antibiotic therapy guidelines can be framed according to local antimicrobial susceptibility trends to improve patient outcomes and minimize antibiotics misuse.

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