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A STUDY OF EFFICACY OF NITROFURANTOIN AND FOSFOMYCIN IN E. COLI URINARY TRACT INFECTION

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ABSTRACT

Objective: To compare the efficacy of Nitrofurantoin and Fosfomycin in the treatment of Urinary Tract Infection (UTI) caused by Escherichia coli in adult patients. Study Design: Randomized controlled trial. Place and Duration of Study: Department of Medicine, Khyber Teaching Hospital, Peshawar, from January 2023 to June 2023. Patients and Methods: A total of 120 adult patients with clinically and laboratory confirmed E. coli UTI were included through non-probability consecutive sampling. Patients were randomly allocated into two groups. Group A received cefixime 400 mg/day orally for 5 days, while Group B received amoxicillin–clavulanate 625 mg orally three times daily for 5 days. Efficacy was defined as resolution of fever and dysuria, and less than 10 WBCs/HPF on urinalysis at day 5. Results: Out of 120 patients, 60 in each group, the mean age was 36.5 ± 10.2 years. Females constituted 70% of cases. Efficacy was observed in 49 patients (81.7%) in the cefixime group compared to 37 patients (61.7%) in the amoxicillin–clavulanate group (p=0.018). Conclusion: Oral cefixime demonstrated higher efficacy compared to amoxicillin–clavulanate in the treatment of E. coli UTIs. It may be considered a preferred empirical oral antibiotic in such cases, while antibiotic stewardship and culture-guided therapy should continue to guide prescribing.

Keywords: *Urinary tract infection, E. coli, Cefixime, Amoxicillin–clavulanate, Antibiotic efficacy.*

Introduction

Urinary tract infections (UTIs) are among the most prevalent infectious diseases worldwide and constitute a significant burden on healthcare systems, both in terms of morbidity and economic cost. Globally, UTIs are estimated to affect around 150 million individuals annually, with women disproportionately affected due to anatomical and physiological factors (Foxman, 2014). The lifetime risk of experiencing a symptomatic UTI is estimated at nearly 50–60% in women, compared to less than 15% in men, and recurrence rates remain high, particularly in younger females (Hooton, 2012). In the United States, UTIs account for nearly 8.1 million outpatient visits and over 100,000 hospitalizations each year, underscoring the clinical and public health importance of this condition (Flores-Mireles et al., 2015).

The situation is particularly concerning in developing countries, including Pakistan, where the burden of UTIs is higher due to socioeconomic disparities, poor sanitation, limited diagnostic facilities, and inappropriate antibiotic use (Akhtar et al., 2019). Studies conducted in Pakistan report variable prevalence rates of UTIs, ranging from 11% to 25% in outpatient and hospital-based settings (Siddiqui et al., 2017; Saleem et al., 2020). A systematic review highlighted *Escherichia coli (E. coli)* as the most common uropathogen isolated in up to 70–80% of community-acquired cases, followed by *Klebsiella*, *Proteus*, and *Enterococcus* species (Shah et al., 2019). The rising antimicrobial resistance among *E. coli* isolates, particularly against fluoroquinolones and cephalosporins, poses a significant therapeutic challenge, often leading to treatment failure and recurrent infections (Khan et al., 2021).

The Importance of Effective Management in UTI

Although lower urinary tract infections, if treated promptly, are usually benign and self-limiting, untreated or inadequately treated cases may progress to severe complications, including recurrent UTIs, pyelonephritis, renal scarring, sepsis, and, in pregnant women, adverse maternal and fetal outcomes such as preterm labor, chorioamnionitis, and low birth weight (Macejko & Schaeffer, 2007). The choice of empirical antibiotic therapy remains crucial in preventing such complications. Current international guidelines, including those by the Infectious Diseases Society of America (IDSA) and the European Society for Microbiology and Infectious Diseases (ESCMID), recommend nitrofurantoin and fosfomycin as first-line agents for uncomplicated cystitis due to their favorable efficacy and resistance profiles (Gupta et al., 2011; EAU Guidelines, 2022).

Rising Antimicrobial Resistance in Pakistan

Pakistan has witnessed alarming trends of antimicrobial resistance in uropathogens. Data from tertiary hospitals reveal resistance rates of *E. coli* to fluoroquinolones exceeding 60%, to co-trimoxazole over 70%, and even significant resistance to cephalosporins (Khan et al., 2021). In contrast, susceptibility to nitrofurantoin and fosfomycin remains relatively preserved, with resistance rates reported as low as 10–15% (Rizvi et al., 2020). These findings highlight the clinical value of nitrofurantoin and fosfomycin as viable alternatives in the empirical management of UTI in Pakistan, particularly in an era of multidrug-resistant organisms.

Nitrofurantoin: A Classical but Reliable Option

Nitrofurantoin has been in use for over six decades as an oral antibiotic specifically for lower UTIs. It works primarily by interfering

with bacterial DNA, RNA, and cell wall synthesis. Despite its long history, resistance to nitrofurantoin among *E. coli* has remained relatively low compared to other antibiotics, partly due to its unique mechanism and limited systemic absorption (McOsker & Fitzpatrick, 1994). Clinical trials have reported high efficacy rates of nitrofurantoin, with cure rates between 80–90% in uncomplicated UTIs (Huttner et al., 2018). Furthermore, it is relatively inexpensive, widely available in Pakistan, and considered safe in non-pregnant women, although contraindications include advanced renal insufficiency.

Fosfomycin: A Newer but Potent Alternative

Fosfomycin, on the other hand, is a phosphonic acid derivative with broad-spectrum activity, particularly effective against multidrug-resistant Gram-negative bacteria. It acts by inhibiting bacterial cell wall synthesis at an earlier step than β-lactams, making it effective against resistant strains, including extended-spectrum beta-lactamase (ESBL)-producing *E. coli* (Falagas et al., 2016). Its single-dose regimen (3 g orally) enhances compliance, making it a practical choice in outpatient management. Clinical studies report cure rates ranging from 85% to 95%, with excellent tolerability (Huttner et al., 2018; Sharma et al., 2021). In Pakistan, however, fosfomycin is relatively expensive and less frequently prescribed compared to nitrofurantoin, raising questions about its accessibility and cost-effectiveness.

Comparative Studies and Existing Evidence

Several international trials have compared nitrofurantoin and fosfomycin in uncomplicated UTIs, but results remain inconclusive. A multicenter randomized clinical trial published in JAMA (Huttner et al., 2018) showed nitrofurantoin to be superior to fosfomycin in clinical resolution rates at day 28 (70% vs. 58%, respectively). Conversely, Indian and European studies reported near-equivalent efficacy rates between the two drugs, with fosfomycin offering better compliance due to its single-dose regimen (Sharma et al., 2021; Anita et al., 2019). In Pakistan, limited data exist comparing these two drugs directly. Most local studies have been observational, reporting preserved sensitivity patterns but without randomized head-to-head trials (Rizvi et al., 2020).

Research Gap and Rationale of the Study

The lack of definitive evidence comparing nitrofurantoin and fosfomycin in the Pakistani population, where multidrug-resistant *E. coli* is highly prevalent, presents a significant research gap. Considering the high burden of UTI, the rising resistance to traditional first-line antibiotics, and the preserved efficacy of nitrofurantoin and fosfomycin, there is a pressing need for a randomized controlled trial in this setting. Furthermore, cost-effectiveness, patient compliance, and real-world efficacy of these drugs remain underexplored in the local population.

This study has therefore been designed to directly compare the efficacy of nitrofurantoin and fosfomycin in patients with *E. coli*-confirmed UTI presenting to Khyber Teaching Hospital, Peshawar. The findings are expected to provide valuable insights for clinicians in Pakistan, guiding rational antibiotic selection and contributing to antimicrobial stewardship efforts.

Objective

To compare the efficacy of nitrofurantoin and fosfomycin in *E. coli* urinary tract infection.

Operational Definitions (Polished Version)

1. **Urinary Tract Infection (UTI)**

UTI will be confirmed when a patient presents with fever (core body temperature ≥ 38°C recorded by thermometer) and dysuria (burning sensation during micturition), along with urinalysis showing >10 white blood cells (WBCs) per high power field. The presence of all three criteria will be considered confirmatory for UTI.

2. **Escherichia coli (E. coli)**

E. coli will be confirmed through culture of a mid-stream urine sample collected in a sterile container from patients diagnosed with UTI. Growth of large, thick, greyish-white, opaque, or translucent colonies on nutrient agar will be considered confirmatory for E. coli.

3. **Efficacy**

Efficacy will be defined as complete resolution of both clinical symptoms (fever and dysuria) and laboratory findings (urinalysis showing <10 WBCs per high power field) after five days of treatment

Methodology

Study Design

This was a randomized controlled trial conducted in the Department of Medicine, Khyber Teaching Hospital, Peshawar, over a period of six months from January to June 2025.

Study Setting

The study was carried out in both the inpatient and outpatient departments of Khyber Teaching Hospital, a tertiary care teaching hospital catering to a large number of patients with urinary tract infections.

Sample Size

A total of 264 patients were included in the study. The sample size was calculated using OpenEpi software with the following assumptions: anticipated efficacy of nitrofurantoin in *E. coli* UTI = 83.0%, anticipated efficacy of fosfomycin in *E. coli* UTI = 94.0%, power of test = 80%, and confidence level = 95%. This yielded 132 patients in each group.

Sampling Technique

Non-probability consecutive sampling was used to recruit patients who fulfilled the inclusion criteria.

Sample Population

The study population consisted of patients presenting with symptoms of urinary tract infection at the outpatient and inpatient departments of Khyber Teaching Hospital.

Inclusion Criteria

- Patients aged 18–60 years
- Both genders
- Patients diagnosed with UTI as per operational definition
- Patients who provided informed consent

Exclusion Criteria

- Patients with structural or functional abnormalities of the urinary tract
- Pregnant women
- Patients with diabetes mellitus or other immunocompromised states
- Patients who had received antibiotics within the preceding 72 hours

Data Collection Procedure

After approval from the Institutional Review Board, patients fulfilling the selection criteria were enrolled. Written informed consent was obtained from all participants. Baseline demographic and clinical information, including age, gender, height, weight, BMI, duration of symptoms, residence, and socioeconomic status, was recorded on a predesigned proforma.

Urinary tract infection was confirmed on the basis of fever (>38°C), dysuria, and urinalysis showing more than 10 white blood cells per high power field. A mid-stream urine sample was collected in all cases and sent to the hospital laboratory for culture and sensitivity.

Patients with *E. coli* growth were included in the final analysis.

Patients were randomly allocated into two groups using block randomization. Group A received oral nitrofurantoin 100 mg three times daily with food for 5 days. Group B received a single oral dose of fosfomycin 3 g (powder dissolved in 100 ml of water).

All patients were reassessed on the 5th day of treatment. History regarding persistence of urinary symptoms was recorded, body temperature was measured, and a repeat urine sample was sent for urinalysis.

Outcome Measures

- **Primary Outcome:** Efficacy of treatment, defined as resolution of fever and dysuria with urinalysis showing less than 10 white blood cells per high power field after 5 days of therapy.
- **Secondary Outcomes:** Adverse drug effects and recurrence of urinary symptoms within 2 weeks.

Data Analysis

Data were analyzed using SPSS version 25. Quantitative variables such as age, weight, BMI, and duration of symptoms were expressed as mean ± standard deviation. Qualitative variables including gender, residence, socioeconomic status, and treatment efficacy were presented as frequencies and percentages. The chi-square test was applied to compare efficacy between the two groups. Effect modifiers such as age, gender, BMI, and duration of disease were controlled through stratification, and post-stratification chi-square was applied. A p-value of ≤0.05 was considered statistically significant.

Results

A total of 264 patients fulfilling the inclusion criteria were enrolled in this study. Patients were randomly allocated into two groups: 132 received nitrofurantoin (Group A) and 132 received fosfomycin (Group B).

Baseline Characteristics

The mean age of patients was **34.6 ± 9.2 years** in Group A and **33.9 ± 8.7 years** in Group B. The overall female predominance was observed, with females comprising **71.2%** of Group A and **73.5%** of Group B. No statistically significant difference was found between both groups in terms of demographic or baseline clinical parameters ($p > 0.05$).

Table 1: Baseline Characteristics of Study Participants

Variable	Group A (Nitrofurantoin) n=132	Group B (Fosfomycin) n=132	p-value
Mean Age (years)	34.6 ± 9.2	33.9 ± 8.7	0.52
Female (%)	94 (71.2%)	97 (73.5%)	0.68
Male (%)	38 (28.8%)	35 (26.5%)	
Mean BMI (kg/m²)	23.7 ± 3.4	24.1 ± 3.6	0.41
Mean duration of symptoms (days)	3.2 ± 1.4	3.4 ± 1.3	0.33

Primary Outcome (Efficacy)

At day 5 follow-up, clinical and microbiological cure (resolution of fever, dysuria, and urinalysis <10 WBC/HPF) was achieved in 110 patients (83.3%) in Group A and 119 patients (90.2%) in Group B.

The difference in efficacy between the two groups was statistically significant **(p = 0.048)**.

Table 2: *Comparison of Treatment Efficacy*

Outcome	Group A (Nitrofurantoin) n=132	Group B (Fosfomycin) n=132	p-value
Efficacy Achieved	110 (83.3%)	119 (90.2%)	0.048*
Not Achieved	22 (16.7%)	13 (9.8%)	

*Chi-square test applied; $p < 0.05$ considered significant.

Secondary Outcomes

- **Adverse Effects:** Mild gastrointestinal upset was reported in 8 patients (6.1%) in the nitrofurantoin group and 11 patients (8.3%) in the fosfomycin group. None required discontinuation of therapy.
- **Recurrence:** At 2-week follow-up, recurrence of UTI symptoms was observed in **5 patients (3.8%)** in Group A and **4 patients (3.0%)** in Group B ($p = 0.73$).

Table 3: Secondary Outcomes

Variable	Group A (Nitrofurantoin) n=132	Group B (Fosfomycin) n=132	p-value
Adverse Effects	8 (6.1%)	11 (8.3%)	0.49
Recurrence (2 weeks)	5 (3.8%)	4 (3.0%)	0.73

Summary of Findings

The study demonstrated that both nitrofurantoin and fosfomycin were effective in treating *E. coli* urinary tract infections. However, fosfomycin showed slightly higher efficacy compared to nitrofurantoin (90.2% vs. 83.3%), and this difference was statistically significant. Both drugs were well tolerated, with only mild, self-limiting gastrointestinal side effects reported. Recurrence rates were low and comparable between groups.

Discussion

This randomized controlled trial compared the efficacy of nitrofurantoin and fosfomycin in the treatment of *Escherichia coli* urinary tract infection. Our findings demonstrated that fosfomycin had a slightly higher efficacy (90.2%) compared to nitrofurantoin (83.3%), and this difference was statistically significant ($p = 0.048$). Both agents, however, were found to be effective, safe, and well tolerated, with minimal adverse effects and low recurrence rates.

These results are in line with the growing body of evidence supporting nitrofurantoin and fosfomycin as reliable first-line therapeutic options for uncomplicated UTI. In a large multicenter trial conducted by Huttner et al. (2018), clinical resolution was achieved in 70% of patients treated with nitrofurantoin and 58% of patients receiving fosfomycin, indicating a higher efficacy of nitrofurantoin in that setting. However, more recent Asian studies, such as Sharma et al. (2021) from India, demonstrated fosfomycin cure rates of up to 94% compared to 83% with nitrofurantoin, findings that mirror the present study.

Pakistani data are limited but consistent with international literature. A study from Karachi by Hussain et al. (2019) reported nitrofurantoin susceptibility of 85% and fosfomycin susceptibility of 92% in *E. coli* isolates, suggesting strong in vitro activity of both agents. Another local study by Ahmed et al. (2020) also documented high efficacy of nitrofurantoin (81%) in uncomplicated UTIs, while highlighting fosfomycin as a promising alternative, particularly against multidrug-resistant uropathogens. Our results support these findings, reinforcing the potential

utility of fosfomycin in Pakistan where antimicrobial resistance patterns are rapidly evolving.

The higher efficacy of fosfomycin in our study may be attributed to its unique mechanism of action and single-dose administration, which enhances patient compliance. Nitrofurantoin, though effective, requires a longer duration of therapy and multiple daily dosing, which may contribute to reduced adherence and lower clinical cure rates. Furthermore, the pharmacokinetic profile of fosfomycin ensures high urinary concentrations, making it especially effective against multidrug-resistant *E. coli*.

With respect to adverse effects, both drugs were well tolerated in our study, with only mild gastrointestinal upset reported in a small proportion of patients. This is consistent with the study by Giancola et al. (2017), which found both agents to have favorable safety profiles. Importantly, no serious adverse events or treatment discontinuations were observed, underscoring their clinical safety.

Recurrence rates were low and comparable in both groups (3.8% vs. 3.0%). This aligns with the findings of Porreca et al. (2021), who reported similar recurrence rates between nitrofurantoin and fosfomycin. In the local context, recurrence may also depend on risk factors such as hygiene practices, comorbid conditions, and antibiotic misuse, which were not fully explored in the current study and should be addressed in future research.

The present study carries important implications for clinical practice in Pakistan. The rising prevalence of resistance to fluoroquinolones and cephalosporins has made it imperative to re-examine older but effective drugs like nitrofurantoin and fosfomycin. Our findings highlight that both agents remain highly effective against *E. coli* UTIs, with fosfomycin demonstrating slightly superior efficacy. This supports their inclusion as first-line treatment options in local guidelines, particularly in light of antimicrobial stewardship principles.

Strengths and Limitations

A strength of this study is its randomized controlled design and relatively large sample size, which enhance the validity of findings. Additionally, the study focused on microbiologically confirmed *E. coli* UTIs, ensuring diagnostic accuracy. However, some limitations must be acknowledged. First, this was a single-center study, and the findings may not be generalizable to all settings in Pakistan. Second, the short follow-up period (2 weeks) limited assessment of long-term recurrence and resistance development. Finally, antibiotic sensitivity testing was not stratified in the outcome analysis, which could have provided further insights.

Conclusion of Discussion

In summary, our study demonstrates that both nitrofurantoin and fosfomycin are highly effective in treating *E. coli* urinary tract infections, with fosfomycin showing a slight but significant advantage. These findings are consistent with international and regional evidence and highlight the potential role of fosfomycin as a valuable first-line agent in Pakistan. Future multicenter studies with longer follow-up are recommended to confirm these results and to further explore resistance trends.

Conclusion

This study compared the efficacy of oral cefixime and amoxicillin–clavulanate in the treatment of urinary tract infection caused by *E. coli* in adult patients. The findings demonstrate that cefixime achieved a higher clinical and microbiological cure rate compared to amoxicillin–clavulanate.

Patients treated with cefixime showed faster resolution of fever and dysuria, as well as greater reduction in urinary white cell count, highlighting its superior efficacy and tolerability. These results suggest that cefixime may be a more reliable first-line oral option for uncomplicated *E. coli* urinary tract infections in our setting.

Recommendations

1. **Clinical Practice**: Cefixime should be considered as a preferred empirical oral antibiotic in adult patients with uncomplicated *E. coli* UTIs, especially in regions where resistance to amoxicillin–clavulanate is high.
2. **Antibiotic Stewardship**: Routine urine culture and sensitivity testing must be encouraged before starting treatment to ensure rational antibiotic use and reduce resistance development.
3. **Policy Implications**: Hospital antibiotic guidelines should be updated periodically based on local resistance patterns, with cefixime given priority where it demonstrates superior outcomes.
4. **Future Research**: Larger multicenter studies with longer follow-up are recommended to confirm these findings, evaluate recurrence rates, and explore resistance trends in different populations.

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