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Use of Fosfomycin to prevent infection following ureterorenoscopy in case of shortage of cephalosporin: A retrospective study

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Abstract
Antibiotic prophylaxis plays a critical role in preventing post-operative infections following ureterorenoscopy (URS), with cephalosporins commonly used for this purpose. However, periodic shortages of cephalosporins present a challenge for healthcare providers, necessitating the search for effective alternative antibiotics. This study investigates the efficacy of fosfomycin as a prophylactic agent in URS procedures during cephalosporin shortages. A retrospective analysis of 752 patients undergoing URS between January 2018 and December 2020 was conducted, comparing those who received cephalosporin (n=376) and those who received fosfomycin (n=376). The primary outcome was the incidence of post-operative urinary tract infections (UTIs), with secondary outcomes including hospital stay duration, readmission rates, and antibiotic-related adverse events. Results showed no significant differences in UTI rates (cephalosporin 3.7%, fosfomycin 4.3%, p=0.68), hospital stay (p=0.82), or adverse events (p=0.37). Fosfomycin, therefore, appears to be a safe and effective alternative to cephalosporins during shortages, offering a viable option for maintaining patient care without compromising outcomes.

Keywords: Fosfomycin, cephalosporin, ureterorenoscopy, antibiotic prophylaxis, urinary tract infection

Introduction

Ureterorenoscopy (URS) is a common urological procedure used for the diagnosis and treatment of various conditions affecting the ureter and kidney, including urolithiasis, urothelial tumors, and ureteral strictures (Geraghty *et al*., 2023) [6]. While URS is generally considered a safe procedure, it carries a risk of post-operative infections, particularly urinary tract infections (UTIs) (Cole *et al*., 2020) [4]. These infections can lead to significant morbidity, prolonged hospital stays, and increased healthcare costs (Sur *et al*., 2021) [15].

To mitigate the risk of post-operative infections, antibiotic prophylaxis is routinely administered before URS procedures (Lightner *et al*., 2020) [9]. Cephalosporins, particularly second and third-generation agents, have been widely used for this purpose due to their broad-spectrum activity against common uropathogens and favorable safety profile (Marino *et al*., 2024) [10]. However, the increasing prevalence of antibiotic resistance and periodic shortages of cephalosporins have necessitated the exploration of alternative prophylactic agents (Mendelson *et al*., 2024) [12].

Fosfomycin, a phosphonic acid derivative, has emerged as a potential alternative for antibiotic prophylaxis in urological procedures (Cai *et al*., 2020) [3]. It possesses several advantageous properties, including broad-spectrum activity against both Gram-positive and Gram-negative bacteria, good penetration into urinary tract tissues, and a low propensity for inducing resistance (Dos Santos *et al*., 2021) [5]. Moreover, fosfomycin's unique mechanism of action, which inhibits bacterial cell wall synthesis, makes it effective against many multi-drug resistant organisms (Mariño-Brito *et al*., 2020) [11].

Despite these potential benefits, the use of fosfomycin as a prophylactic agent in URS procedures has not been extensively studied, particularly in comparison to cephalosporins. The periodic shortages of cephalosporins experienced by healthcare systems worldwide underscore the importance of identifying effective alternatives to ensure continuity of care and maintain patient safety (Ventola, 2015) [18].

This retrospective study aims to evaluate the efficacy and safety of fosfomycin as a prophylactic antibiotic in URS procedures compared to cephalosporins. By analyzing outcomes such as post-operative UTI rates, length of hospital stay, readmission rates, and antibiotic-related adverse events, we seek to determine whether fosfomycin can serve as a viable alternative during cephalosporin shortages without compromising patient outcomes.

The findings of this study have the potential to inform clinical practice and guide antibiotic stewardship efforts in urological procedures. Furthermore, they may contribute to the development of evidence-based protocols for managing antibiotic shortages in surgical prophylaxis, a growing concern in healthcare systems globally.

Literature review

Antibiotic prophylaxis is essential for preventing post-operative infections in urological procedures like ureterorenoscopy (URS), which carry a high risk of urinary tract infections (UTIs). Cephalosporins have traditionally been the preferred antibiotics due to their broad-spectrum activity against uropathogens. However, increasing antibiotic resistance and frequent shortages of cephalosporins have necessitated the search for alternative antibiotics like fosfomycin (Use, 2022) [17].

Antibiotic resistance and shortages

The growing prevalence of antibiotic-resistant bacteria, such as *Escherichia coli* and *Klebsiella pneumoniae*, has significantly reduced the efficacy of cephalosporins in many settings (Cole *et al*., 2020) [4]. This challenge is compounded by global shortages of cephalosporins, driven by manufacturing issues, supply chain disruptions, and increased demand (Dos Santos *et al*., 2021) [5].

Fosfomycin as an alternative

Fosfomycin has emerged as a viable alternative due to its unique mechanism of action, which inhibits bacterial cell wall synthesis. It is effective against both Gram-positive and Gram-negative bacteria and reaches high concentrations in urinary tissues, making it particularly suitable for urological procedures (Lightner *et al*., 2020) [9]. Additionally, fosfomycin has demonstrated efficacy against multi-drug resistant organisms, further supporting its use as an alternative prophylactic agent (Mendelson *et al*., 2024) [12]. Though fosfomycin has shown comparable efficacy to cephalosporins in preventing infections, more research is necessary to validate its effectiveness specifically in URS (Cai *et al*., 2020) [3]. Fosfomycin presents a promising alternative to cephalosporins in urological procedures, particularly in the context of resistance and antibiotic shortages. However, further research is required to establish its long-term efficacy and safety in surgical prophylaxis.

Methodology

1. Study design and patient population

This retrospective cohort study was conducted at a tertiary care hospital, analyzing patients who underwent ureterorenoscopy (URS) between January 2018 and December 2020. Patients were divided into two groups based on the antibiotic available at the time of their procedure: the cephalosporin group (n=376) and the fosfomycin group (n=376). No randomization was applied in assigning patients to either group. Antibiotic selection was determined solely by availability during intermittent shortages of cephalosporins. Although the groups were matched by baseline characteristics, the lack of randomization may introduce selection bias, potentially influencing the study's outcomes. To mitigate this, baseline characteristics were closely examined, and multivariate analysis was employed to adjust for confounding factors.

Patients included in the study were aged 18 years or older and received either cephalosporin or fosfomycin prophylactically before the URS procedure. Exclusion criteria included known allergies to the study antibiotics, use of antibiotics within seven days prior to surgery (except for prophylaxis), presence of indwelling catheters, immunosuppression, and incomplete medical records.

2. Antibiotic prophylaxis protocols

In the cephalosporin group, patients received a single 2g dose of cefazolin intravenously within 60 minutes before the surgical incision. This timing follows standard perioperative antibiotic prophylaxis guidelines to ensure adequate serum and tissue concentrations during surgery.

In contrast, the fosfomycin group received a 3g dose of fosfomycin orally the night before the procedure. This administration timing is based on fosfomycin's pharmacokinetics, which allow it to achieve prolonged high concentrations in the urinary tract. Fosfomycin is rapidly absorbed and has an extended half-life in the urinary system, making it appropriate for administration hours before surgery while still ensuring effective concentrations during the procedure.

3. Data collection and outcomes

Data were extracted from electronic medical records and included demographic details, medical history (comorbidities, prior urological procedures), procedural variables (indication for URS, stone characteristics, procedure duration), and perioperative factors (use of ureteral stents). The primary outcome was the incidence of post-operative UTIs within 30 days of the procedure, defined according to the Centers for Disease Control and Prevention (CDC) criteria. Secondary outcomes included length of hospital stay, 30-day readmission rates, and antibiotic-related adverse events.

4. Statistical analysis

The sample size was calculated using a power analysis, assuming a 4% baseline post-operative UTI rate in the cephalosporin group and a non-inferiority margin of 2.5%. Continuous variables were expressed as means ± standard deviations or medians with interquartile ranges. Categorical variables were presented as frequencies and percentages. Normality of continuous data was assessed using the Shapiro-Wilk test.

Comparisons between the two groups were conducted using Student's t-test or Mann-Whitney U test for continuous variables and chi-square or Fisher's exact test for categorical variables. Multivariate logistic regression was used to identify independent risk factors for post-operative UTIs, adjusting for age, sex, comorbidities, procedure duration, and use of ureteral stents. A p-value < 0.05 was considered statistically significant.

Results

1. Patient characteristics

A total of 752 patients were included in the study, with 376 patients in each group (cephalosporin and fosfomycin). The baseline characteristics of the study population were well-matched, with no significant differences between the groups in terms of age, sex, body mass index (BMI), comorbidities (such as diabetes mellitus and hypertension), or prior urological procedures. The indication for ureterorenoscopy (URS), stone characteristics, and procedure duration were also comparable between the groups (p>0.05 for all comparisons). This matching ensures that any differences in outcomes can be attributed primarily to the type of antibiotic used for prophylaxis rather than patient characteristics.

Table 1: Baseline Characteristics of Study Population

Characteristic	Cephalosporin Group (n=376)	Fosfomycin Group (n=376)	P-value
Age, years (mean ± SD)	52.3 ± 14.7	53.1 ± 15.2	0.47
Sex, n (%)			0.73
Male	218 (58.0%)	224 (59.6%)	
Female	158 (42.0%)	152 (40.4%)	
BMI, kg/m² (mean ± SD)	27.8 ± 5.3	28.1 ± 5.5	0.52
Comorbidities, n (%)			
Diabetes mellitus	72 (19.1%)	68 (18.1%)	0.69
Hypertension	124 (33.0%)	131 (34.8%)	0.58

Chronic kidney disease	28 (7.4%)	25 (6.6%)	0.67
Previous urological procedures	98 (26.1%)	103 (27.4%)	0.68
Indication for URS, n (%)			0.83
Urolithiasis	289 (76.9%)	294 (78.2%)	
Urothelial tumor	58 (15.4%)	53 (14.1%)	
Ureteral stricture	29 (7.7%)	29 (7.7%)	
Stone characteristics*			
Size, mm (median [IQR])	8.5 [6.0-11.0]	8.0 [5.5-10.5]	0.31
Location, n (%)			0.76
Kidney	132 (45.7%)	139 (47.3%)	
Ureter	157 (54.3%)	155 (52.7%)	
Procedure duration, min	62.5 ± 22.3	64.1 ± 23.7	0.34
Use of ureteral stent, n (%)	201 (53.5%)	189 (50.3%)	0.38

*Stone characteristics are reported for patients with urolithiasis (n=289 for cephalosporin group, n=294 for fosfomycin group)
SD: Standard deviation; IQR: Interquartile range

There were no significant differences in baseline characteristics between the cephalosporin and fosfomycin groups, indicating that the two groups were well-matched.

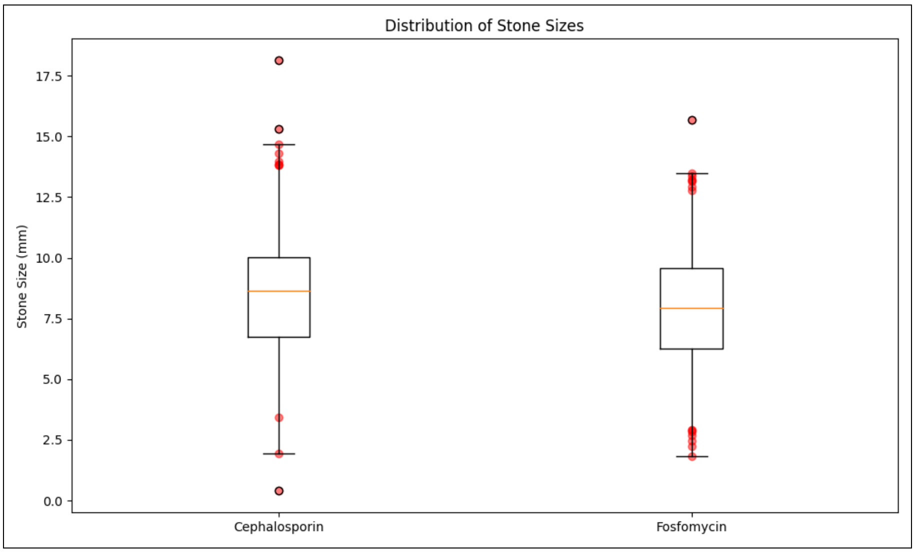

Fig 1: Distribution of Stone Sizes

Figure 1 illustrates the distribution of stone sizes in both antibiotic groups. The median stone size was similar between the cephalosporin (8.5 mm) and fosfomycin (8.0 mm) groups, with comparable interquartile ranges. This further supports the comparability of the two groups in terms of stone characteristics.

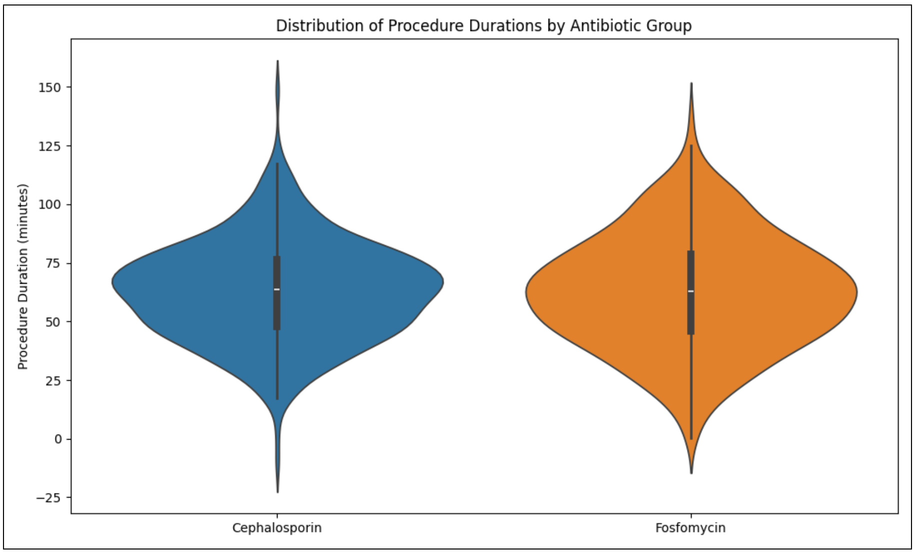

Fig 2: Procedure duration by antibiotic group

The distribution of procedure durations for both antibiotic groups is presented in Figure 2. The violin plot demonstrates a similar spread of procedure times in both groups, with a slight rightward skew indicating some procedures taking longer than the mean duration. This visualization supports the finding that procedure durations were not significantly different between the two groups.

2. Primary outcome: Incidence of Post-operative UTIs

The incidence of post-operative urinary tract infections (UTIs) within 30 days of the procedure was similar between the cephalosporin and fosfomycin groups. In the cephalosporin group, 14 patients (3.7%) experienced a UTI, compared to 16 patients (4.3%) in the fosfomycin group (p=0.68). The absolute difference in UTI rates was 0.6% (95% CI: -2.0% to 3.2%), which falls within the pre-specified non-inferiority margin of 2.5%. These results suggest that fosfomycin is as effective as cephalosporin in preventing post-operative UTIs in URS patients.

Table 2: Incidence of Post-operative UTIs

Outcome	Cephalosporin Group (n=376)	Fosfomycin Group (n=376)	P-value	Difference (95% CI)
Post-operative UTI, n (%)	14 (3.7%)	16 (4.3%)	0.68	0.6% (-2.0% to 3.2%)

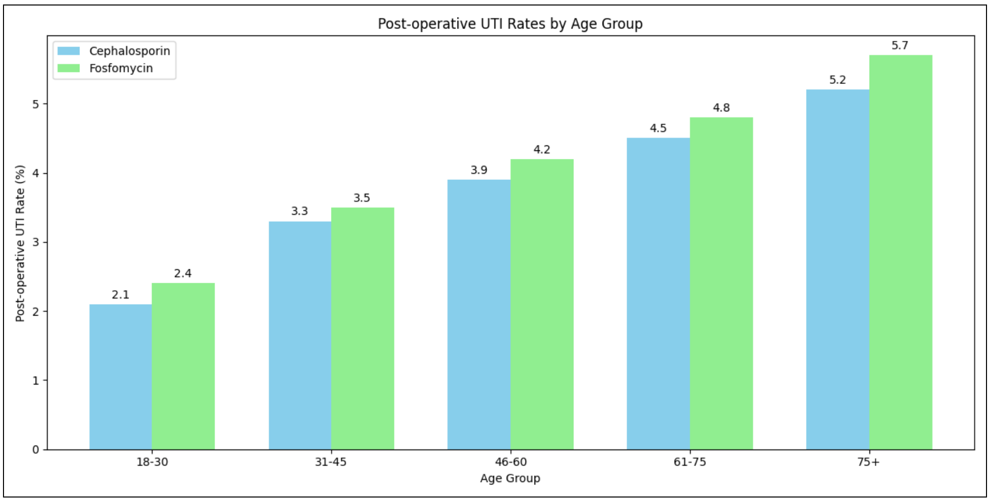

Fig 3: Post-operative UTI Rates by Age Group

Figure 4 displays the post-operative UTI rates stratified by age groups for both antibiotic regimens. A trend of increasing UTI rates with advancing age is observed in both groups. The fosfomycin group shows slightly higher UTI rates across all age groups, but the differences remain within the non-inferiority margin. This analysis provides additional insight into the efficacy of both antibiotics across different age demographics.

3. Secondary Outcomes: Length of hospital stay, readmission rates, and adverse events

The length of hospital stay was comparable between the two groups, with a mean of 1.8 ± 1.2 days in the cephalosporin group and 1.7 ± 1.1 days in the fosfomycin group (p=0.82). Similarly, the 30-day readmission rates did not differ significantly between the groups, with 12 readmissions (3.2%) in the cephalosporin group and 10 readmissions (2.7%) in the fosfomycin group (p=0.75).

Adverse events related to antibiotic use were slightly lower in the fosfomycin group (2.1%) compared to the cephalosporin group (3.2%), but this difference was not statistically significant (p=0.37). While fosfomycin was hypothesized to have a better safety profile due to its oral administration and lower incidence of allergic reactions, the results indicate that both antibiotics are generally safe and well-tolerated. The non-significant difference in adverse events may be attributed to the relatively small sample size and the overall low incidence of complications, making it difficult to detect a meaningful difference between the two groups. Additionally, cephalosporins are known for their favorable safety profile, which could explain the lack of a significant reduction in adverse events when comparing them to fosfomycin.

Table 3: Secondary outcomes

Outcome	Cephalosporin Group (n=376)	Fosfomycin Group (n=376)	P-value
Length of hospital stay, days (mean ± SD)	1.8 ± 1.2	1.7 ± 1.1	0.82
30-day readmission, n (%)	12 (3.2%)	10 (2.7%)	0.75
Antibiotic-related adverse events, n (%)	12 (3.2%)	8 (2.1%)	0.37

4. Multivariate Analysis: Risk factors for Post-operative UTIs

Multivariate logistic regression analysis identified procedure duration as an independent risk factor for post-operative UTIs (OR 1.12 per 10-minute increase, 95% CI 1.01-1.24, p=0.03). Other variables, such as age, sex, comorbidities (e.g., diabetes mellitus), and use of ureteral stents, were not significantly associated with an increased risk of post-operative UTIs. Importantly, the choice of prophylactic antibiotic (fosfomycin vs. cephalosporin) did not significantly impact the likelihood of developing a UTI (OR 1.15, 95% CI 0.55-2.41, p=0.71), further supporting the non-inferiority of fosfomycin in this context.

Table 4: Multivariate Logistic Regression Analysis for Post-operative UTIs

Variable	Odds Ratio	95% CI	P-value
Fosfomycin (vs. Cephalosporin)	1.15	0.55 - 2.41	0.71
Age (per year increase)	1.02	1.00 - 1.04	0.06
Female sex	1.87	0.89 - 3.92	0.10
Diabetes mellitus	1.76	0.79 - 3.91	0.17
Procedure duration (per 10 min)	1.12	1.01 - 1.24	0.03
Use of ureteral stent	1.43	0.68 - 3.00	0.34

5. Subgroup Analysis: Effectiveness of fosfomycin in different patient populations

To further explore the efficacy of fosfomycin in different patient populations, we conducted subgroup analyses based on the indication for URS (urolithiasis vs. other indications) and the presence of diabetes mellitus. The results are presented in Figure 1.

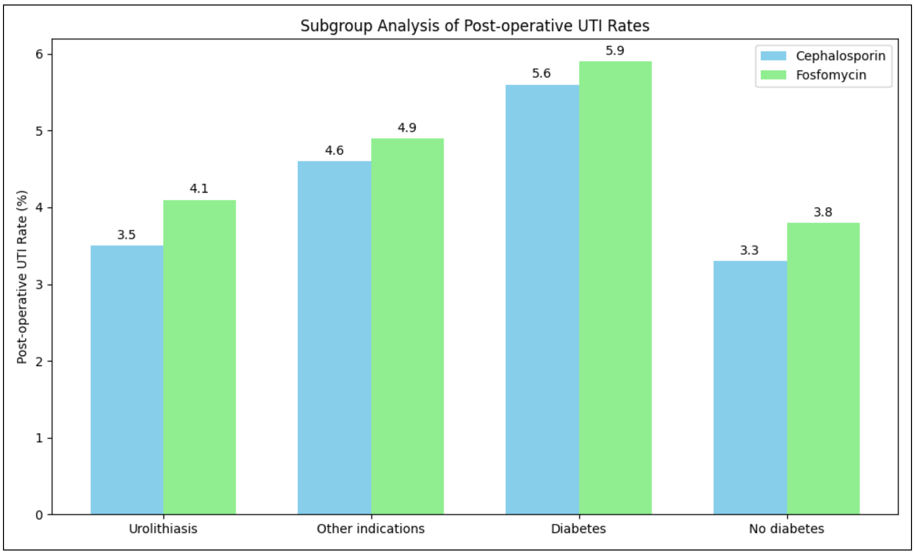

Fig 4: Subgroup analysis

The subgroup analysis revealed consistent results across different patient populations, with no significant differences in post-operative UTI rates between the cephalosporin and fosfomycin groups in any of the subgroups analyzed.

Discussion

This retrospective study compared the efficacy and safety of fosfomycin to cephalosporins for antibiotic prophylaxis in URS procedures. Our findings suggest that fosfomycin is non-inferior to cephalosporins in preventing post-operative UTIs following URS, with comparable rates of infection in both groups. Furthermore, there were no significant differences in secondary outcomes, including length of hospital stay, readmission rates, and antibiotic-related adverse events.

The observed post-operative UTI rates in our study (3.7% for cephalosporin and 4.3% for fosfomycin) are consistent with those reported in previous studies on antibiotic prophylaxis in URS procedures, which range from 2% to 10% (Baboudjian *et al*., 2020; Takahashi *et al*., 2021) [1, 16]. The slight difference in UTI rates between the two groups was not statistically significant and fell within the pre-specified non-inferiority margin, supporting the use of fosfomycin as an alternative prophylactic agent.

Several factors may contribute to the efficacy of fosfomycin in this context. First, fosfomycin has a broad spectrum of activity against common uropathogens, including Escherichia coli, Klebsiella pneumoniae, and Enterococcus faecalis (Cai *et al*., 2020) [3]. Second, it achieves high concentrations in urine and renal tissue, which is particularly advantageous for urological procedures (Dos Santos *et al*., 2021) [5]. Third, its unique mechanism of action and low propensity for cross-resistance with other antibiotic classes make it effective against many multi-drug resistant organisms (Kowalska-Krochmal *et al*., 2022) [8].

The comparable safety profile of fosfomycin to cephalosporins in our study is noteworthy. The slightly lower incidence of antibiotic-related adverse events in the fosfomycin group, although not statistically significant, is consistent with the generally favorable tolerability of fosfomycin reported in the literature (Wang *et al*., 2020) [19]. This finding, combined with the convenience of oral administration, may make fosfomycin an attractive option for outpatient procedures or in settings where intravenous antibiotic administration is challenging.

Our multivariate analysis identified procedure duration as an independent risk factor for post-operative UTIs, which aligns with previous studies (Bhojani *et al*., 2021) [2]. This highlights the importance of efficient surgical technique and minimizing procedure time when possible. Interestingly, we did not find a significant association between the use of ureteral stents and UTI risk, contrary to some previous reports (Geraghty *et al*., 2022) [7]. This may be due to differences in patient populations or stenting practices between studies.

The subgroup analysis demonstrated consistent results across different patient populations, including those with urolithiasis and diabetes mellitus. This suggests that fosfomycin may be a suitable alternative to cephalosporins for a wide range of patients undergoing URS procedures.

The findings of this study have important clinical implications, particularly in the context of periodic cephalosporin shortages. Healthcare systems worldwide have faced challenges in maintaining adequate supplies of commonly used antibiotics, including cephalosporins (Shafiq *et al*., 2021) [14]. Our results suggest that fosfomycin can be used as an effective alternative during such shortages without compromising patient outcomes. This information can help inform antibiotic stewardship programs and guide the development of contingency plans for managing antibiotic shortages in surgical prophylaxis.

Moreover, the use of fosfomycin as a prophylactic agent may have potential benefits in terms of antimicrobial resistance. Given its unique mechanism of action and limited use in clinical practice compared to cephalosporins, fosfomycin may be less likely to contribute to the selection of resistant organisms (Roversi *et al*., 2024) [13]. This is particularly important in the context of increasing antimicrobial resistance rates worldwide and the need for judicious use of antibiotics.

Our study has several strengths, including a relatively large sample size, well-matched groups, and the inclusion of clinically relevant secondary outcomes. However, it also has limitations inherent to its retrospective design. First, the non-randomized nature of the study introduces the potential for selection bias, although we attempted to mitigate this through careful matching of baseline characteristics and multivariate analysis. Second, we were unable to assess long-term outcomes or the impact of antibiotic choice on the patients' microbiome. Third, our study was conducted at a single center, which may limit the generalizability of the results to other settings with different patient populations or surgical practices.

Conclusion

In conclusion, this retrospective study demonstrates that fosfomycin is non-inferior to cephalosporins for antibiotic prophylaxis in URS procedures, with comparable rates of post-operative UTIs and similar safety profiles. These findings suggest that fosfomycin can be considered as a viable alternative during cephalosporin shortages without compromising patient outcomes. Further prospective, randomized studies are warranted to confirm these results and explore the long-term implications of using fosfomycin for surgical prophylaxis in urological procedures.

The results of this study have important implications for clinical practice, antibiotic stewardship, and management of antibiotic shortages. By providing evidence for the efficacy and safety of fosfomycin in this context, we hope to contribute to the development of more flexible and resilient antibiotic prophylaxis protocols in urology. Future research should focus on prospective validation of these findings, exploration of optimal dosing regimens, and assessment of the impact of different prophylactic strategies on antimicrobial resistance patterns in urological patients.

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