Internal Medicine Residents' Perceptions of Fosfomycin use – a Brief Report

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Abstract—

Background: *Fosfomycin is approved by the FDA for treating uncomplicated cystitis caused by Escherichia coli and Enterococcus faecalis. However, it is often prescribed off-label for broader indications, with limited data on physician knowledge and practice patterns.*

Methods: *We surveyed residents in the Yale New Haven Internal Medicine Residency program across three teaching hospitals to assess awareness, prescribing habits, and perceived indications for fosfomycin.*

Results: *Seventy-eight residents responded (58% response rate); 89.7% were familiar with fosfomycin, and 71.4% had prescribed it. The most common indication was uncomplicated cystitis (94.3%), followed by pyelonephritis (41.4%) and prostatitis (32.9%). E. coli (71.4%) and Klebsiella pneumoniae (68.6%) were the most frequently selected organisms. Only 30% correctly identified uncomplicated cystitis as the sole FDA-approved indication, and no responses fully aligned with the approved spectrum of use.*

Conclusion: *Internal medicine trainees demonstrated significant gaps in knowledge regarding fosfomycin's approved role. Educational efforts are needed to promote judicious prescribing and preserve its effectiveness against multidrug-resistant pathogens.*

Keywords— Fosfomycin, Antibiotic stewardship, Urinary tract infection (UTI), Multidrug-resistant organisms (MDRO), Off-label prescribing, Internal medicine trainees, Extended-spectrum beta-lactamases (ESBL), Antimicrobial resistance.

I. BACKGROUND

Fosfomycin, discovered in the 1960s, is a synthetic, broad-spectrum, bactericidal antibiotic which works by inhibiting the enzyme MurA, an essential for bacterial cell wall synthesis [1]. Fosfomycin is available as an oral suspension in the United States, and the pharmacokinetics allow for one-time dosing [2], making it a good oral option, especially in the outpatient setting for treating urinary tract infections (UTI). Fosfomycin is approved by the U.S. Food and Drug Administration (FDA) to treat uncomplicated cystitis caused by *Escherichia coli (E. coli)* and *Enterococcus faecalis (E. faecalis)* in women [2].

We noticed that non-infectious disease specialists prescribe fosfomycin to treat various conditions outside of its FDA approved indications, including complicated cystitis, pyelonephritis, long-term UTI prophylaxis, and prostatitis. In addition, it was also used to target many other organisms such as *Klebsiella pneumoniae, Proteus mirabilis, Enterobacter cloacae complex, Pseudomonas aeruginosa,* etc. Despite a few anecdotal successful cases, no extensive data is available for off-label uses, which

begs the question of the nescience surrounding the usage of fosfomycin. This analysis aimed to assess the understanding of fosfomycin use among internal medicine trainees at a tertiary academic institution.

II. METHOD AND FINDINGS

The Yale New Haven Internal Medicine Residency program trains about 140 residents at any time. We conducted this survey at three main teaching hospitals via online and in-person questionnaire surveys among the residents (Supplementary Material 1)

We received responses from 78 participants across four training years (Table 1). Overall response rate was 58%. Of the 70 participants who had previously known about fosfomycin, 50 had prescribed the medication in both inpatient and outpatient settings. The most common clinical indication selected was uncomplicated cystitis (94.3%), followed by pyelonephritis (41.4%) and prostatitis (32.9). Eighteen participants (25.7%) selected bacteremia. *E. coli* was the most chosen pathogen (71.4%), followed by *Klebsiella pneumoniae* (68.6%). Nineteen residents selected all extended-spectrum beta-lactamases (ESBL) producing Gram-negative bacteria. Among Gram-positive organisms, *Staphylococcus aureus* was chosen at the highest rate (28.6%), followed by Coagulase-negative *Staphylococcus* (24.3%), and *E. faecalis* (22.9%) (Table 2). Twenty-one participants indicated uncomplicated cystitis as the only indication where fosfomycin should be used. No participants chose E. faecalis and E. coli by themselves as targeted pathogens. Consequently, no participant showed a response that was in accordance with the fosfomycin's approved FDA label of fosfomycin.

TABLE 1
PARTICIPANT DEMOGRAPHICS

Parameter	Subjects (n = 78)
Post graduate year, n (%)	
PGY 1	40 (51.3)
PGY 2	20 (26.6)
PGY 3	15 (19.2)
PGY 4	3 (3.9)
Training track, n (%)	
Preliminary	9 (11.5)
Primary care	6 (7.7)
Categorical	63 (80.8)
Residents who had known of fosfomycin	
Yes	70 (89.7)
No	8 (10.3)

TABLE 2
SURVEY OUTCOMES

Parameter	Subjects (n = 70)
Residents who had prescribed fosfomycin	
Yes	50 (71.4)
No	20 (28.6)
Clinical indication chosen	
Uncomplicated cystitis	66 (94.3)
Pyelonephritis	29 (41.4)
Prostatitis	23 (32.9)
UTI prophylaxis	19 (27.1)
Bacteremia	18 (25.7)
Other	0
Organism indication chosen	
Staphylococcus aureus	20 (28.6)
Coagulase negative *Staphylococcus*	17 (24.3)
Enterococcus faecalis	16 (22.9)
All Gram-positive bacteria	7 (10)
Escherichia coli	50 (71.4)
Klebsiella pneumoniae	48 (68.6)
Enterobacter spp.	16 (22.9)
Pseudomonas aeruginosa	28 (40)
All ESBL Gram-negative bacteria	19 (27.1)
All Gram-negative bacteria	10 (14.3)
Other	1 (1.4)

UTI: urinary tract infection
ESBL: extended spectrum beta-lactamases

III. DISCUSSION

Increases in drug resistance have limited oral treatment options available for lower UTIs. *E. coli* and other gram-negative organisms that harbor ESBL are often resistant to oral beta-lactams, trimethoprim-sulfamethoxazole, and fluoroquinolones [3]. Fosfomycin is a good option for uncomplicated cystitis secondary to ESBL *E. coli* and an alternative treatment option for ESBL *E. coli* prostatitis [5].

Fosfomycin can also be an acceptable alternative for salvage therapy for UTIs caused by multidrug- resistant organisms (MDRO) [4]. Fosfomycin exhibits in-vitro activity against a large number of bacteria. However, the clinical significance is unknown. It is important to recognize that many organisms, including *Pseudomonas aeruginosa*, *Morganella* species, *Proteus vulgaris* and *Staphylococcus saprophyticus* have elevated minimum inhibitory concentration (MIC) values and are unlikely to respond to fosfomycin. Clinical and Laboratory Standards Institute breakpoints are only available for *E. coli* and *E. faecalis* [5]. Fosfomycin is not recommended for treating infections outside the urinary tract, such as bacteremia, or pyelonephritis due

to its inadequate concentrations at other sites [5]. Due to the intricacy of these clinical and microbiological indications, fosfomycin should be carefully considered on a case-by-case basis, preferably in conjunction with an infectious disease consultation when used outside of its FDA approval.

Our results raised concerns about the insufficient understanding of fosfomycin usage among internal medicine residents at our institution. The most noteworthy findings were related to the medication's off-label usage, Gram-positive coverage and extra urinary tract indications. In this era of increasing antibiotic resistance and infections secondary to MDRO, judicial use of fosfomycin is crucial so that it remains a viable option for treating patients with ESBL *E. coli* urinary tract infections. We hope that this work will serve as a foundation for future educational opportunities for the next generation of healthcare professionals on the accurate usage of this unique antibiotic. Furthermore, this study could be expanded to include other medical and surgical specialties and different levels of practitioners.

IV. STUDY QUESTIONNAIRE

Please circle your answers:

Your Initials:

A. Post graduate year PGY1 PGY2 PGY3 PGY4 PGY5 Other (please specify)

B. Internal Medicine Track

1. Traditional/Categorical
2. Preliminary
3. Primary care
4. Other (please specify)

C. Have you heard of fosfomycin?

1. Yes
2. No (please skip D, E and F)

D. Have you prescribed fosfomycin.

1. Yes
2. No

E. When do you think we should use fosfomycin (indications)? Select all that apply.

1. Uncomplicated cystitis	4. Recurrent UTI prophylaxis
2. Pyelonephritis	5. Bacteremia
3. Prostatitis	6. Other (please describe)

F. Which organisms can you treat with fosfomycin? Select all that apply.

1. *Staphylococcus aureus*	7. *Enterobacter cloacae complex*
2. Coagulase negative *Staphylococcus*	8. *Pseudomonas aeruginosa*
3. *Enterococcus faecalis*	9. All ESBL Gram-negative bacteria
4. All Gram- positive bacteria	10. All Gram- negative bacteria
5. *E. coli*	11. Other (please describe)
6. *Klebsiella pneumoniae*	

V. CONCLUSION

This study highlights notable gaps in knowledge regarding fosfomycin use among internal medicine residents, particularly in relation to its limited FDA-approved indication and lack of established efficacy for non-urinary tract infections or Gram-positive organisms. The frequent selection of off-label uses, including pyelonephritis, bacteremia, and broad Gram-negative or Gram-positive coverage, underscores the risk of inappropriate prescribing. Given the increasing prevalence of multidrug-resistant organisms and the importance of preserving oral treatment options, fosfomycin should be used judiciously and primarily within its approved indications. Educational interventions aimed at improving awareness of antimicrobial stewardship principles are essential to ensure responsible prescribing practices. Future research should expand these assessments across other specialties and healthcare settings to better inform strategies that safeguard the clinical utility of Fosfomycin.

AUTHOR DECLARATION

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TL – contributed to preparing and distributing surveys, statistical analysis, literature review, writing of the manuscript and processing of suggestions by co-authors in the subsequent drafts.

DBN – contributed to statistical analysis, edits of manuscript.

TB – contributed to preparing surveys, literature review, edits of manuscript.

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