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Fosfomycin for UTI Therapy - *The Secret is Leaking Out*

Introduction

Incidence of community-onset infections caused by *Enterobacteriaceae* that produce extended-spectrum beta-lactamases (ESBLs) has been steadily increasing in the United States over the past two decades. For example, a 2020 CDC report covering a cohort of 890 hospitals found an over 50% increase in incidence of ESBL infections between 2012 and 2017, which was largely driven by community-onset cases.[1] This trend has been coupled with an increase in ESBL-producing isolates that are resistant to fluoroquinolones and trimethoprim-sulfamethoxazole: up 60-90% of ESBL-producing *E. coli* were resistant to both of these antibiotic options in some U.S. cohorts, compared to just 1-3% in the late 2000s.[2-4] Remaining options for oral therapy of ESBL UTIs are largely limited to nitrofurantoin and fosfomycin, though neither are FDA-approved for complicated UTI therapy.

More data regarding fosfomycin use in the treatment of UTIs continue to emerge, particularly in the realm of therapy for complicated UTIs. In this newsletter, we will review two recent clinical studies and discuss potential advantages and pitfalls with its use in UTIs.

Overview and Role in Uncomplicated UTI Therapy

First isolated from strains of *Streptomyces* in 1969, fosfomycin has potent antibacterial properties with relatively low human toxicity. Fosfomycin interferes with peptidoglycan synthesis through its unique inhibition of the MurA enzyme, which is a critical step in bacterial cell wall synthesis. While *Pseudomonas aeruginosa* and *Acinetobacter baumannii* are often resistant, fosfomycin has shown notable *in vitro* bactericidal activity against a multitude of both Gram-positive and Gram-negative organisms, and due to its target of action independent of penicillin-binding protein, fosfomycin can be used in the treatment of ESBL producing organisms.[5-7]

Fosfomycin has several other characteristics that makes it an attractive agent for UTIs. It penetrates biofilms and a variety of human tissues, including urinary tract organs like the bladder, kidneys, and prostate. In the U.S., fosfomycin is available in an oral formulation that retains around 40% bioavailability, and around 30-60% of the oral version of the drug is excreted unchanged in the urine.[7,14] Compounded with a long 4- to 8-hour half-life, one could see the appeal of fosfomycin as a single-dose option for uncomplicated UTI therapy. Most available studies and meta-analyses of available randomized trials suggest that single-dose fosfomycin is a non-inferior and well-tolerated therapy for uncomplicated UTIs, particularly for those with ESBL-producing *E. coli*.[5-10, 14]

Despite these features, wider use of fosfomycin is currently limited by a few issues. First, the Clinical and Laboratory Standards Institute (CLSI) only provides susceptibility breakpoints for fosfomycin against *E. coli* at this time, which limits its use against other organisms in the U.S. Second, given its rare use, the availability of fosfomycin susceptibility testing may vary hospital-to-hospital, and like other antibacterials, bacterial resistance remains a topic of concern. [5-7, 11] Finally, the cost of fosfomycin is a limiting factor in many situations, as insurance companies often do not cover it currently; on the other hand, it may be more affordable when considering costs and complications of outpatient IV antibiotic therapy.

Usual dosing recommendations for fosfomycin in uncomplicated UTI is a 3-gram dose given once, though multi-dose regimens (e.g., 3 grams every 48 to 72h for 3 doses) have been described. Common side effects include diarrhea, nausea, abdominal pain, dyspepsia, and headaches.

Fosfomycin in Complicated UTIs

The role of fosfomycin in complicated UTIs has been suggested by a few prior studies, but two additional studies were published in 2021 that further suggest it

may be an effective stepdown therapy in complicated UTIs.

Fosfomycin versus Ciprofloxacin as Stepdown Therapy for Febrile UTI in Women

A 2021 double-blind, randomized control trial compared the non-inferiority of fosfomycin to ciprofloxacin as step-down therapy among febrile *E. coli* UTI in women.[12] Once afebrile for 24-48 hours, adult women receiving 2-5 days of empiric IV therapy for febrile *E. coli* UTI were randomized to twice-daily ciprofloxacin 500mg or once-daily 3g fosfomycin (notably an atypical dosing regimen) with an additional placebo dose for total of 10 days. The study initially intended to enroll 240 subjects to allow for multivariate sub-analysis, but due to logistical and financial constraints posed by COVID-19, the trial was halted at a total enrollment of 97 patients.

The fosfomycin and ciprofloxacin groups had similar baseline characteristics (including Charslon Comorbidity scores as well as rates of *E. coli* bacteremia, urosepsis, and pyelonephritis), except the fosfomycin group had higher incidence of diabetes while the ciprofloxacin group had higher incidence of nephrolithiasis. The *E. coli* isolates had to demonstrate susceptibility to both ciprofloxacin and fosfomycin for inclusion; these isolates were resistant to amoxicillin-clavulanic acid in 28% of included patients, resistant to trimethoprim-sulfamethoxazole in 21% of patients, and ESBL-producing in 6% of patients.

Compared to the ciprofloxacin group, the fosfomycin group had non-inferior clinical cure rates (75% for fosfomycin, 65% for ciprofloxacin) defined as reduction of symptoms at 6-10 days post-treatment without requirement for additional antibiotics. There were similar findings in the post-hoc analysis of patients with *E. coli* bacteremia, with respect to additional antibiotic therapy, hospital readmission, ICU admission, or any cause mortality.[12]

Fosfomycin versus Ertapenem for Complicated UTI

In addition, a 2021 retrospective cohort study examined the comparative efficacy of oral fosfomycin therapy to ertapenem therapy in the stepdown or transition to outpatient treatment of complicated UTIs from the hospital.[13] Three hundred twenty-two patients were included in the final analysis. The fosfomycin and ertapenem groups were demographically similar, except for a higher proportion of patients with bacteremia and pyelonephritis without percutaneous nephrostomy tubes (PCNTs) among the ertapenem group. The fosfomycin group, on the other hand, included more patients with indwelling urinary catheters, nephrolithiasis, and other urinary obstructions (like BPH or penile edema). Both groups had high rates of ESBL-producing organisms (84.6% and 91.0% among the fosfomycin and ertapenem groups respectively) and lacked other oral options for therapy.

Overall, the fosfomycin and ertapenem groups had statistically similar 30-day clinical success rates, defined as the resolution of symptoms without relapse by 30 days of follow-up. Clinical success in the fosfomycin group did not vary with duration of lead-in IV therapy or dosing intervals. Furthermore, the fosfomycin-treated group had shorter durations of hospitalization, IV therapy, post-discharge therapy, and total antibiotic therapy overall. Adverse events were rare in both groups, but numerically fewer events were observed with fosfomycin as compared to ertapenem therapy (1 versus 10 adverse events). On multivariate analysis, it should be noted that infection in setting of PCNTs were associated with high rates of failure as compared to pyelonephritis alone in the fosfomycin group. In addition, nephrolithiasis was associated with both recurrence of symptoms at last follow-up and relapse within 3 months regardless of the treatment.[13]

Discussion and Summary

Fosfomycin has an emerging set of data supporting its use in the therapy in the therapy of UTIs, particularly in the setting of ESBL-producing *E. coli* infections. A few points should be considered with its use however:

- CLSI breakpoints for susceptibility testing for fosfomycin are currently only available for *E. coli*
- Availability of susceptibility testing for fosfomycin may vary across institutions
- Cost and insurance coverage for fosfomycin may be limited for patients

- While one of the studies reviewed in this newsletter did include patients who only received fosfomycin for the duration of their therapy, further studies are needed to evaluate its role as the sole agent for *E. coli* complicated UTI therapy, and this practice is currently not recommend.

Given the above, coupled with the growing concern for emergence of resistance, perhaps fosfomycin might best be reserved for therapy of known ESBL *E. coli* uncomplicated UTIs or stepdown therapy of ESBL *E. coli* complicated UTIs when 1) no other oral options are available, 2) IV therapy is an unfavorable option, and 3) susceptibilities are ideally available. Fosfomycin therapy might best be avoided in complicated UTIs involving PCNTs based on the studies above. More study is required to evaluate fosfomycin's clinical efficacy as monotherapy in complicated UTIs as well as its effectiveness against organisms besides *E. coli*.

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