Current key topics in fosfomycin

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Oral and intravenous fosfomycin in complicated urinary tract infections

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ABSTRACT

Urinary tract infections are one of the most common health problems and entail a high consumption of health system resources. Due to the increase in global antibiotic resistances in recent years, it is increasingly common to find uropathogens with multiple resistance mechanisms, including quinolone-resistant bacteria, broad-spectrum β-lactamase producers and carbapenemase producers. In this scenario, the role of fosfomycin has gained considerable importance, given its spectrum of activity against multidrug resistant microorganisms (Gram-positive and Gram-negative), becoming an attractive alternative therapy. Regarding the use of fosfomycin in complicated urinary tract infections, there is increasing clinical experience with patients with infections caused by multidrug resistant bacteria, those with recurrent urinary tract infection and special populations such as those with kidney transplants. Randomized comparative studies and series are underway, which will provide greater evidence. Nevertheless, more studies are needed to confirm the enormous potential of fosfomycin in complicated urinary tract infection in the era of multiresistance.

Keywords: Fosfomycin, Urinary tract infection, Multiresistance, Extended-spectrum beta–lactamase.

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MAGNITUDE OF COMPLICATED URINARY TRACT INFECTIONS IN THE ERA OF MULTIDRUG RESISTANCE

Urinary tract infections (UTI) are one of the most common health problems affecting humans, with an estimated global incidence rate of approximately 18 episodes per 1000 person-years, considering only the community-acquired cases [1]. The high economic impact of UTI on health systems is therefore not surprising, with an estimated cost of $424 million to $1.6 billion per year [2].

Various methods for classifying UTI have been proposed based on the location of acquisition, the anatomical site of the infection and the presence of risk factors in the host, differentiating in this case between uncomplicated and complicated UTI (cUTI). The latter of which is considered an infection that occurs in male, elderly, patients with kidney transplants (KT), functional or anatomical urinary tract impairment, presence of urinary catheters and/or azotemia due to intrinsic kidney disease [3, 4]. Recurrent UTI is also considered complicated. The importance of differentiating between cUTI and uncomplicated UTI lies in the fact that the former are associated with the isolation of bacteria other than *Escherichia coli* and that are relatively more resistant to antibiotics [1]. These patients therefore have a greater likelihood of receiving inadequate treatment and experiencing treatment failure, recurrence, relapses, complications and death [5, 6]. Additionally, cUTI is characterized by longer treatments with broader spectrums than uncomplicated UTI [7, 8].

THE MICROBIOLOGY OF COMPLICATED URINARY TRACT INFECTION

Although the spectrum of uropathogens involved in cUTI can vary with the geographical pattern, the period and the type of patient being studied, among other aspects, it has generally been observed that although *E. coli* is still one of the most common uropathogens in cUTI, the role of other Gram-negative microorganisms such as *Klebsiella* spp., *Enterobacter cloacae*, *Serratia marcescens*, *Proteus* spp. and *Pseudomonas aeruginosa* is growing. Gram-

positive bacteria such as enterococci, *Staphylococcus* spp. and *Candida* spp. are also frequently isolated. The indiscriminate use of antibiotics in recent years has changed the susceptibility profile of antibiotics typically employed to treat UTIs, such as β-lactams and fluoroquinolones. Various studies have reported fluoroquinolone resistance by *E. coli* and *K. pneumoniae* ranging from 7% to 56%, as well as an increase in extended-spectrum β-lactamase (ESBL)-producing and AmpC-producing microorganisms, with the consequent resistance or reduced susceptibility to β-lactams [9-13]. In the multicenter Spanish study ITUBRAS-GEIH published in 2013, 13% of healthcare-related bacteremic UTIs were caused by ESBL-producing enterobacteria, and 30% had reduced susceptibility to amoxicillin-clavulanate [6]. It is therefore not surprising that in recent years the so-called "old antibiotics" such as polymyxins, aminoglycosides and fosfomycin have gained importance in clinical practice.

FOSFOMYCIN: MAIN CHARACTERISTICS

Fosfomycin is an antibiotic derived from phosphonic acid, initially isolated in 1969 through cultures of *Streptomyces* spp. [14]. Fosfomycin has a bactericidal action through the inhibition of the UDP-N-acetylglucosamine-3-0-enolpyruvyl transferase (MurA) enzyme in the first steps of peptidoglycan synthesis in the bacterial wall [15]. Fosfomycin also acts by reducing the adherence of bacteria to some epithelia, such as the urinary epithelium [16]. The antibiotic has also shown an immunomodulatory effect by suppressing the production of tubular necrosis factor-β and a number of interleukins (IL-1β, IL-2, IL-8, etc.), as well as improving the phagocytic activity of neutrophils [17]. With regard to its action on biofilms, previous studies on animal models have shown that fosfomycin not only

decreases or eradicates biofilms but can also modify their structure *per se*. Fosfomycin has been studied alone and in combination with other antibiotics, such as vancomycin and quinolones, for treating infections caused by *Staphylococcus* spp. [18] and *P. aeruginosa*, respectively [19].

Currently, fosfomycin is available in three formulations, two of which are oral in the form of fosfomycin trometamol (granules in packages of 2 or 3 g) and fosfomycin calcium (500-mg hard gelatin capsules) and one of which is intravenous as fosfomycin disodium (from 1 g to 8 g with succinic acid as the excipient) (figure 1).

FOSFOMYCIN'S SPECTRUM OF ACTIVITY AGAINST UROPATHOGENS

Fosfomycin's *in vitro* activity has been assessed against a broad spectrum of Gram-positive and Gram-negative microorganisms. Fosfomycin has considerable activity against *E. coli*, *Klebsiella* and *Enterobacter* spp., *Proteus mirabilis*, *Shigella* spp., *Serratia* spp., *Citrobacter* spp. and *Salmonella* spp. [20-22]. Given its lack of cross-resistance, fosfomycin is active against multidrug-resistant enterobacteria, ESBL/carbapenemase-producing enterobacteria and also bacteria resistant to quinolones and cotrimoxazole (table 1). This property means that the drug is highly useful and places it at the forefront in the era of multidrug resistance. Previous studies have shown that 81-100% of ESBL-producing *E. coli* strains are still susceptible to fosfomycin [23, 24]. For *Klebsiella* spp., the proportion is generally somewhat lower, although 95.2% have been shown to be susceptible in a number of studies [25]. *Morganella morganii* is inherently fosfomycin-resistant [26]. The antibiotic is considered active against *Enterococcus* spp. and *Staphylococcus*

Table 1	Fosfomycin susceptibility in studies since 2010		
Resistance profile	Microorganism	Number of studies (study period)	% Fosfomycin susceptibility
ESBL-producing *Enterobacteriaceae*	*E. coli*	30 (2010-2017)	81-100
	K. pneumoniae	13 (2011-2015)	40-95.2
	Proteus spp.	2 (2014)	50-72
	E. cloacae	1 (2010)	97
	S. marcenses	1 (2010)	84
	C. freundii	1 (2010)	95
Gram-negative bacteria with reduced resistance or susceptibility to carbapenems	*K. pneumoniae* KPC	3 (2010-2015)	39.2-99
	P. aeruginosa	1 (2013)	80.6
Multidrug-resistant *Enterobacteriaceae*	*E. coli*	2 (2010-2012)	98.8-100
	K. pneumoniae	1 (2010)	90.5
Gram-positive	*S. aureus*	3 (2010-2013)	33.2-99.6; SARM 68.9-93.3
	E. faecalis	1 (2013)	96
	E. faecium	2 (2013)	76-100

KPC, *Klebsiella pneumoniae* carbapenemase; MRSA, methicillin-resistant *Staphylococcus aureus*.
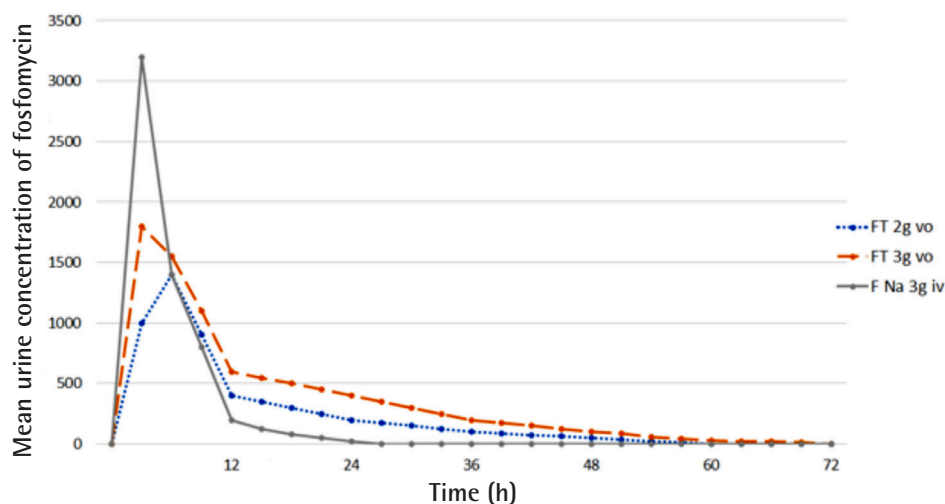
| Figure 1 | Mean urine concentration of fosfomycin after 2 and 3g of fosfomycin trometamol (FT) oral (vo) and 3 g of intravenous (iv) fosfomycin disodium (F Na). Adapted from Bergen et al [45]. |

spp., regardless of methicillin-resistance [20], except against *Staphylococcus capitis* and *Staphylococcus saprophyticus,* which are inherently fosfomycin-resistant. Fosfomycin has activity against *Listeria monocytogenes, Neisseria gonorrhoeae, Aerococcus urinae* and *Helicobacter pylori* [27-30]. In terms of its anaerobicide activity, fosfomycin has shown efficacy against *Peptococcus* spp. and *Peptostreptococcus* spp. but not against *Bacteroides* spp. [31]. *Acinetobacter* spp., *Stenotrophomonas maltophilia*, *Burkholderia cepacia* and *Mycobacterium tuberculosis* are considered inherently fosfomycin-resistant [32, 33]. Regarding fosfomycin susceptibility of *P. aeruginosa*, a cutoff point has not been established. Previous studies have considered as susceptible isolates with a MIC ≤64 mg/L, extrapolating from enterobacteria's CLSI cutoff [33, 34]. Table 1 summarizes the fosfomycin susceptibility in the most relevant studies conducted from 2010 to the present.

MECHANISMS OF RESISTANCE

The mechanisms of fosfomycin resistance do not usually confer cross-resistance to other microorganisms. The inherent resistance is based on an amino acid replacement in *murA* (e.g., *Mycobacterium tuberculosis*) [32] or on peptidoglycan recycling in the formation of the bacterial wall instead of *de novo* synthesis through the UDP-N-acetylglucosamine-3-0-enolpyruvyl transferase enzyme (*Pseudomonas* spp.) [35]. Moreover, acquired fosfomycin resistance usually develops from mutations in the genes that code for the fosfomycin transporters (*glpT, uhpT*) in such a way that fosfomycin is hindered or blocked from entering the cells [36]. Other less common mechanisms are based on fosfomycin-modifying enzymes such as FosA [37], FosB [38], FosC [39] and FosX [40], as well as other plasmids that confer co-resistance to other antibiotics such as β-lactams, aminoglycosides and quinolones [25, 41, 42].

PHARMACOKINETICS AND PHARMACODYNAMICS OF FOSFOMYCIN IN URINARY TRACT INFECTION

The absorption of oral fosfomycin occurs in the small bowel [43], with fosfomycin trometamol presenting an oral bioavailability of 34-58% [20]. The calcium formulation is hydrolyzed with the gastric acid. The extent of absorption is therefore lower than that of the trometamol formulation (12-37%) [44]. Approximately 93-99% of fosfomycin is excreted unaltered in urine, and the compound barely binds to plasma proteins, spreading widely to tissues in the kidneys, bladder and noninflamed prostate [43].

Previous studies have assessed the plasma and urinary concentrations of fosfomycin at various dosages and formulations [45]. For example, maximum concentrations in urine are reached 2 h after administering a 3-g dose of fosfomycin trometamol orally, with concentrations between 1,053 mg/L and 3,749 mg/L, maintaining a mean concentration above 128 mg/L (standardized cutoff between intermediate susceptibility and complete susceptibility) for at least 36 h (figure 1). Figure 1 shows that urinary concentrations of fosfomycin disodium drop below 128 mg/L in the first 12 h after intravenous administration, reflecting the long period of oral absorption for fosfomycin trometamol. Despite the improved oral bioavailability with the trometamol formulation, maximum plasma concentrations are still far below those achieved with the intravenous formulation of fosfomycin disodium: 2.5 h after the administration of 3 g of fosfomycin trometamol, the C_{max} is 21.8 ± 4.8 mg/L, with an area under the curve (AUC) of 144.9 ± 40.5 mg·h/L. The values reached with a 3-g intravenous dose of fosfomycin disodium are a C_{max} of 370.6 ± 92 mg/L and an AUC of 443.6 ± 48.9 mg·h/L [45].

FOSFOMYCIN IN ANIMAL MODELS OF URINARY TRACT INFECTION

Fosfomycin has been tested in a number of murine UTI models. A study was recently published that assessed the PK/PD indices of fosfomycin in murine models with ascending UTI by ESBL-producing, AmpC-producing and carbapenemase-producing *E. coli*. In this study, there was a significant reduction in the number of colony-forming units/mL of fosfomycin-susceptible *E. coli*, including multidrug-resistant strains [46]. Using murine UTI models, Lefort et al. assessed the combination of fosfomycin and cefoxitin on susceptible strains of ESBL CTX-M-15-producing *E. coli* versus fosfomycin in monotherapy. The authors found that combined therapy was beneficial in terms of sterilization and reducing the bacterial count [47].

CLINICAL EXPERIENCE WITH FOSFOMYCIN FOR TREATING COMPLICATED URINARY TRACT INFECTIONS

Oral fosfomycin. A single 3-g dose of fosfomycin trometamol is recommended as one of the first-line treatments for uncomplicated UTI, especially in women and for infections caused by *E. coli* [48]. Although the literature is scarce and highly heterogeneous, there is some clinical experience with cUTI. However, to date there have been no published randomized clinical trials that have evaluated the efficacy of fosfomycin trometamol in cUTI. The Dutch study FORECAST is currently awaiting its start [49]. This randomized, double-blind, noninferiority clinical trial will compare oral sequencing (after having undergone at least 48 h of intravenous treatment) with 500 mg of ciprofloxacin every 12 h versus 3 g of fosfomycin trometamol every 24 h for a total of 10 days in 240 women with febrile community-acquired UTI caused by *E. coli*. The primary endpoint is the clinical response at 6-10 days post-treatment. Other factors will also be assessed, such as mortality, microbiological eradication and adverse effects.

Various studies have sought to assess the efficacy of multiple doses of fosfomycin trometamol in cUTI (recurrent and/or caused by multidrug-resistant microorganisms). With regard to prospective studies, Mozdzan et al. assessed the efficacy of fosfomycin trometamol (3 g every 30 days for 12 months) versus nitrofurantoin (administered every 12 h for 7 days and then every night for 12 months) in postmenopausal women with diabetes and recurrent lower UTI, with 50 patients assigned to each group. At 3 months, 89% and 91% of the trometamol and nitrofurantoin groups, respectively, were asymptomatic, 90% and 92% were asymptomatic at 6 months, and 88% and 88% were asymptomatic at 12 months [50]. Lu-Dong Qiao et al. [51] prospectively and multicentrically assessed the efficacy of three 3-g doses of fosfomycin trometamol administered on days 1, 3 and 5 of the study. The patients were clinically and microbiologically evaluated on days 8 and 15. The study included 335 patients, 105 (29%) of whom were men; 67 (20%) patients presented lower cUTI, and 79 (23%) presented recurrent UTI. The ratio of clinical effectiveness was 73%, 63% and 77%, respectively. In terms of microbiological eradication, 77% of the patients with cUTI and 63% of those with recurrent UTI achieved eradication. A third study

prospectively assessed the efficacy of three 3-g doses of fosfomycin trometamol versus intravenous carbapenem for 14 days in patients with lower cUTI produced specifically by ESBL *E. coli*. The study included 47 patients (27 treated with fosfomycin and 20 with carbapenems), with similar baseline characteristics. At least 76% of the patients presented more than one complication, the most common of which were the presence of a urinary catheter, prior surgery and malignancy in the urinary tract. Although there were no statistically significant differences between the groups in terms of clinical and microbiological cure assessed between days 7 and 9 from the end of treatment, both rates were lower in the group treated with fosfomycin than in the group treated with carbapenems: 77.7% and 59.3% for the fosfomycin group and 95% and 80% for the carbapenem group, respectively [52] three times. Pullukcu et al. [53] three times also assessed the use of 2 or more doses of fosfomycin trometamol in patients with UTI by ESBL *E. coli*. The authors retrospectively included 52 patients, 36 of whom had cUTI criteria: urinary catheter, KT, urinary tract abnormality (nephrolithiasis or malignancy) and/or recent manipulation at this level. Clinical cure and microbiological eradication was achieved in 94.3% and 78.5% cases, respectively, with no significant differences in terms of cUTI versus uncomplicated UTI (p>0.05).

Regarding the study of infections by other multidrug-resistant microorganisms, Neuner et al. [54] assessed the ratio of microbiological cure in patients with UTIs by carbapenemase-producing *K. pneumoniae*, *P. aeruginosa*, ESBLs and vancomycin-resistant *Enterococcus* spp. treated with fosfomycin trometamol. The authors retrospectively included 41 patients, 80% of whom presented a complication risk factor: catheter, recent urological surgery, recurrent UTI and neurogenic bladder. There was a significant number of patients with solid organ transplants (n=15). The patients were administered a mean of 2.9 ± 1.8 doses of 3-g fosfomycin, and 27% were also administered another antibiotic treatment in combination with fosfomycin. The authors observed a 59% overall microbiological cure rate, which was less frequent in the patients with solid organ transplants (21%, p=0.02). The microbiological eradication rate varied according to the MIC of fosfomycin (24/35 in isolates with MIC ≤128 mg/L and 0/3 with MIC ≥256 mg/L). In the cases of UTI by carbapenemase-producing *K. pneumoniae* and *P. aeruginosa*, the authors observed a discrepancy between the *in vitro* susceptibility and the microbiological cure (92% vs. 46% and 75% vs. 38%, respectively).

Sastry et al. [55] conducted a retrospective study with hospitalized patients who were administered at least one dose of fosfomycin trometamol. The authors included 537 patients, 286 of whom had cUTI factors: male sex (81, 15%), urinary catheter carriers (162, 30%) and immunosuppression (124, 23%). Nevertheless, only 396 (74%) patients were administered fosfomycin in the context of a UTI. The most frequently employed regimen was fosfomycin in single dose, although 19 patients were administered more than one dose in intervals of 24-72 h. Two groups were differentiated according to whether the UTI diagnosis was performed based on medical criteria (n=239) or on the National Healthcare Safety Network (NHSN) definitions (n=89). The authors found a clinical curing rate of 74.8% and 87.5%, respectively. In both groups, the authors found that the

antecedent of having undergone surgery in the 30 days prior to the administration of fosfomycin was a factor associated with clinical failure (p<0.005). For the group that met the NHSN definitions, the presence of a urinary catheter for more than 48 h (p<0.04) was a factor associated with clinical failure.

Regarding the use of fosfomycin specifically in KT, a recently published retrospective study assessed 53 episodes in this population treated with fosfomycin trometamol in monotherapy for lower UTI (n=33) or as oral sequencing in upper UTI (n=5). The clinical cure rate was 67% and 80%, respectively [56]. Pink et al. [57] reported the concomitant use of fosfomycin trometamol and double carbapenem therapy for patients with transplants and cUTI by *K. pneumoniae* with New Delhi metallo-β-lactamase (NDM) in KT.

The efficacy of oral fosfomycin has been shown in the extended treatment of chronic prostatitis in line with reasonably good prostatic penetration [58]. Los Arcos et al. [59] published 15 cases of chronic prostatitis with good response to oral fosfomycin trometamol. Seven patients had a clinical response, and 8 had persistent microbiological eradication after 6 weeks of oral fosfomycin trometamol (3 g every 48 or 72 h). Microbiological eradication was achieved in 4 of 5 patients who had multidrug-resistant enterobacterial infection. In another article, 2 patients with prostatitis due to multidrug-resistant microorganisms were cured after being administered a daily dose of 3 g of fosfomycin trometamol for 12-16 weeks, with good tolerance [60]. In both cases, the fosfomycin concentrations were measured (approximately 5 mg/L). The 3-g doses twice daily were intolerable due to the adverse gastrointestinal effects [61].

Given its reduced oral bioavailability [44], the fosfomycin calcium formulation is not indicated for cUTI, and there is no published experience on this topic.

Intravenous fosfomycin. Until a few years ago, the evidence on the use of fosfomycin disodium was based on heterogeneous studies, most of which were retrospective or case series and were conducted in Europe or Japan [62].

The results of the ZEUS study were recently published. The multicenter, phase II/III, randomized, double-blind clinical trial compared fosfomycin disodium (6 g every 8 h) versus piperacillin/tazobactam (P/T, 4.5 g every 8 h), both of which were administered in a 1-h infusion to patients with cUTI or acute pyelonephritis. Sequencing to oral administration was not possible, and those patients who presented concomitant bacteremia had to complete 14 days of treatment. The authors randomized 465 patients (233 to fosfomycin and 231 to P/T; 1 patient was excluded in P/T branch due to not receiving at least 1 dose of study drug) and found that fosfomycin was not inferior to P/T in the overall response (primary endpoint) (64.7% [119/184] vs. 54.5% [97/178], respectively, with a difference of 10.2% [95% CI -0.4, 20.8]). The clinical and microbiological cure rates were similar between the groups: 90.8% (167/184) for fosfomycin versus 91.6% (163/178) for P/T and 66% (127/184) for fosfomycin and 57.3% (102/178) for P/T, respectively. Fosfomycin was very well tolerated; most of the adverse effects were mild and temporary and included hypokalemia and increased transaminase levels [63].

Another randomized, open, phase III clinical trial (FOREST; NCT02142751) is currently underway comparing fosfomycin versus meropenem in bacteremic urinary infections by ESBL *E. coli* or quinolone-resistant *E. coli*. The patients are randomized to receive 4 g of fosfomycin disodium intravenously every 6 h in a 60-min infusion or 1 g of meropenem every 8 h in 15-30-min infusions. Sequencing to oral administration can be performed on day 5 to fosfomycin trometamol (3 g every 48 h) in the first group and to ciprofloxacin, amoxicillin/clavulanate or cotrimoxazole, according to the antibiogram, in the second group. Both groups are to complete 10 to 14 days of treatment [64].

Intravenous fosfomycin in cUTI could also be useful in combination with other antimicrobials, especially for cases of infection by multidrug-resistant or extremely drug-resistant bacteria [65]. Synergy has been observed in 10-60% of *P. aeruginosa* strains with ticarcillin, piperacillin, azlocillin, ceftazidime, aztreonam, imipenem, ciprofloxacin, pefloxacin and amikacin [66, 67]. Several studies have tested fosfomycin in combination with meropenem, colistin, aztreonam and several aminoglycosides in carbapenemase-producing enterobacteria. Synergy has been demonstrated between fosfomycin and meropenem, colistin, gentamicin and plazomicin against a number of strains of *E. coli* and Verona integron-mediated metallo-β-lactamase (VIM)-producing and NDM-producing *K. pneumoniae*. The prevention of resistance selection has also been demonstrated in combinations with fosfomycin [68-71].

In summary, the current studies are heterogeneous, and we lack high quality clinical trials and studies to confirm the enormous potential of fosfomycin in the era of multidrug resistance, especially in cUTI.

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