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Fosfomycin: Resurgence of An Old Companion

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Abstract

Fosfomycin was discovered over four decades ago, yet has drawn renewed interest as an agent active against a range of multidrug-resistant (MDR) and extensively drug-resistant (XDR) pathogens. Its unique mechanism of action and broad spectrum of activity makes it a promising candidate in the treatment of various MDR/XDR infections. There has been a surge of *in vitro* data on its activity against MDR/XDR organisms, both when used as a single agent and in combination with other agents. In the United States, fosfomycin is only approved in an oral formulation for the treatment of acute uncomplicated urinary tract infections (UTIs), whereas in some countries both oral and intravenous formulations are available for various indications. Fosfomycin has minimal interactions with other medications and has a relatively favorable safety profile, with diarrhea being the most common adverse reaction. Fosfomycin has low protein binding and is excreted primarily unchanged in the urine. The clinical outcomes of patients treated with fosfomycin are favorable for uncomplicated UTIs, but data are limited for use in other conditions. Fosfomycin maintains activity against most *Enterobacteriaceae* including *Escherichia coli*, but plasmid-mediated resistance due to inactivation have appeared in recent years, which has the potential to compromise its use in the future. In this review, we summarize the current knowledge of this resurgent agent and its role in our antimicrobial armamentarium.

Keywords

phosphonic acid; multidrug resistance (MDR); extensive drug resistance (XDR); susceptibility testing; plasmid-mediated resistance; pharmacokinetics; combination therapy; clinical outcome

In the current era of antimicrobial resistance, the family *Enterobacteriaceae* is one of the most problematic groups of pathogens. Many classes of antimicrobial agents used to be almost uniformly active against *Enterobacteriaceae*, including β -lactam- β -lactamase inhibitor combinations, cephalosporins, carbapenems, sulfonamides, fluoroquinolones and aminoglycosides. However, resistance to these classes has worsened substantially in the last

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decade. Taking *E. coli* as an example as the prototypical and the most common *Enterobacteriaceae* implicated in human infections, approximately half of those causing UTI among inpatients are now resistant to ampicillin-sulbactam, a third are resistant to ciprofloxacin, and up to 10% are resistant to cephalosporins, primarily due to production of extended-spectrum- β -lactamase (ESBL) [1]. Notably, this worsening resistance with the spread of ESBL is occurring not only in healthcare-associated infections [2, 3] but also community-associated infections [4, 5].

Urinary tract infection (UTI) is an exceedingly common type of bacterial infection that affects healthy individuals as well as those with comorbidities around the world. It is estimated that one in every three women experience at least one episode of urinary tract infection (UTI) requiring treatment with antimicrobial agents by the age of 24 [6]. Given the increasing rates of resistance in urinary pathogens to agents commonly used to treat UTIs such as trimethoprim-sulfamethoxazole and ciprofloxacin, there has been a surging interest in identifying new treatment options or re-evaluate existing agents for the treatment of UTIs. One such agent is fosfomycin, which has been in existence for over four decades now. Its use has gained popularity especially since the Infectious Diseases Society of America (IDSA) and the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) updated their guidelines for the treatment of acute uncomplicated UTI and pyelonephritis in women by recommending fosfomycin as one of the first-line agents for the treatment of uncomplicated UTIs in 2011 [7]. Fosfomycin is a phosphonic acid derivative that was first identified and reported from various strains of *Streptomyces* spp. in 1969 [8]. It has been in use in most European countries for many years, but was only approved by the Food and Drug Administration (FDA) in the United States to be used, in the oral form only, as fosfomycin tromethamine, for the treatment of uncomplicated cystitis in 1996.

This review article summarizes recent studies describing the mechanism of action and resistance, susceptibility testing, pharmacodynamics and pharmacokinetic properties, dosing considerations, and clinical outcome data related to the use of this agent, including infections caused by multidrug-resistant (MDR) or extensively drug-resistant (XDR) pathogens.

Mechanism of action and resistance

Fosfomycin was initially reported as phosphonomycin, a broad-spectrum cell wall synthesis inhibitor produced by *Streptomyces fradiae*, *Streptomyces viridochromogenes*, and *Streptomyces wedmorensis* from the Merck, Sharp & Dohme Research Laboratories in 1969 [8]. Fosfomycin is in an antimicrobial class of its own and is structurally unrelated to any other agent currently approved for clinical use (Figure 1). Its mode of action is inactivation of the cytosolic N-acetylglucosamine enolpyruvyl transferase (MurA), thereby preventing the formation of N-acetylmuramic acid from N-acetylglucosamine and phosphoenolpyruvate, which is the initial step in peptidoglycan chain formation of the bacterial wall [9]. Hence, fosfomycin is bactericidal in nature. The mechanisms by which fosfomycin is transported across the bacterial permeability barrier have been well described. Fosfomycin primarily utilizes the glycerol-3-phosphate transport system (GlpT) as a method of entry in almost all susceptible bacteria [10]. In addition, the hexose phosphate uptake

transport system (UhpT) is induced in the presence of glucose-6-phosphate, providing an alternative to the GlpT system for its influx into cells [11].

Key resistance mechanisms to fosfomycin include the loss or reduced production of these functional transporters, reduced affinity to MurA and production of fosfomycin-modifying enzymes (Table 1). The former two mechanisms are chromosomal, whereas the latter mechanism can be chromosomal or plasmid-mediated. Mutations or insertional inactivation in one or both of the chromosomally-encoded transporter genes (*glpT* and/or *uhpT*) or their regulatory genes *uhpA*, *uhpB* and *uhpC* of the UhpT system can lead to the loss of function of these transporters and resistance to fosfomycin [12]. Modification of MurA, the target of the drug has also been reported to result in fosfomycin resistance. In *E. coli*, fosfomycin covalently binds to cysteine at position 115 of MurA. The substitution of cysteine with aspartate in this active site has been shown to result in resistance to fosfomycin [13, 14]. The overexpression of MurA is another mechanism that can contribute to the development of a fosfomycin-resistant phenotype [15]. However, resistance due to MurA modification or overexpression appears to be rarer compared with the aforementioned transporter-mediated mechanisms.

Fosfomycin-modifying enzymes can be chromosomally encoded but are may also be encoded on transferable plasmids, especially in *E. coli* [16, 17]. Three of the four known groups of fosfomycin modifying enzymes, namely FosA, FosB, and FosX, function by nucleophilic attack on carbon atom 1 of fosfomycin to open the epoxide ring thus rendering the drug inactive. The enzymes encoded by these genes differ by the identity of the nucleophile utilized in the reaction: glutathione for FosA [18], bacillithiol for FosB [19], and water for FosX [20]. In general, FosA and FosX enzymes are produced by Gram-negative bacteria, whereas FosB is produced by Gram-positive bacteria. Another group of plasmid-mediated fosfomycin modifying enzymes, FosC, utilizes ATP and adds a phosphate group to fosfomycin, thus altering its properties and inactivating the drug [21].

Among these groups of Fos enzymes, the most concerning from an epidemiological standpoint is plasmid-mediated FosA3 in *E. coli*. FosA3 was initially reported from an *E. coli* clinical strain identified in Japan in 2006 [22], but has subsequently been shown to be widespread in East Asia (China, Hong Kong, Korea and Japan), in ESBL-producing *E. coli* and less commonly in *K. pneumoniae* from humans as well as food animals and pets [23–27]. The *fosA3* gene is typically located on a composite transposon bounded by two copies of IS26 on a conjugative plasmid that also carries a CTX-M-type ESBL [28]. Therefore, *E. coli* that acquires such a plasmid becomes resistant to cephalosporins and fosfomycin simultaneously. More recently, 34% of KPC-producing *K. pneumoniae* collected from hospitals in China were shown to be resistant to fosfomycin and carried *fosA3* [29]. Sequencing of a representative plasmid showed *bla*_{KPC-2} and *fosA3* to be located on the same plasmid, which is worrisome since fosfomycin may be lost as a potential treatment option for KPC-producing organisms if such plasmids continue to spread.

Another Fos enzyme of potential concern is FosB3 in *Enterococcus faecium* which is reported in China [30]. *fosB3* can be co-located with *vanA* on self-transmissible plasmids; therefore, acquisition of such plasmids can result in simultaneous resistance to fosfomycin

and vancomycin [31]. Some fosfomycin-resistant *Staphylococcus* strains including *Staphylococcus aureus* carry plasmid-mediated *fosB*, though data are limited on this topic [32, 33].

Susceptibility testing

Susceptibility testing of fosfomycin merits attention (Table 2). The Clinical and Laboratory Standards Institute (CLSI) endorses reporting of fosfomycin susceptibility for urinary tract isolates of *E. coli* and *Enterococcus faecalis* with the use of agar dilution method or disk diffusion method [34]. The current susceptibility breakpoint of fosfomycin is 64 µg/ml for MIC and 16 mm for disk diffusion. The agar dilution method should be performed with Mueller-Hinton agar medium supplemented with 25 µg/ml of glucose-6-phosphate to reduce the rates of false resistance [35]. For disk diffusion testing and Etest, the addition of glucose-6-phosphate in the medium is not required since the disks and the gradient strips are supplemented with it. The European Committee on Antimicrobial Susceptibility Testing (EUCAST) defines the susceptibility breakpoint as 32 µg/ml for *Enterobacteriaceae* and *Staphylococcus* spp. (the latter for intravenous formulation only) (<http://www.EUCAST.org>). Addition of glucose-6-phosphate is required under the EUCAST guidelines as well. The testing methods (agar dilution, disk diffusion and Etest) appear to correlate well among contemporary gram-negative clinical isolates, with some Etest and agar dilution results not in essential agreement but not resulting in significant major or very major error rates [36], while some data suggest that disk diffusion testing and Etest may undercall resistance for carbapenem-resistant *P. aeruginosa* [37] and *Enterobacteriaceae* [38].

One practical challenge in interpreting the results of diffusion based methods (Etest and disk diffusion) is the frequent observation of scattered colonies within the inhibition zones [38, 39]. The CLSI recommends measuring the colony-free inner zone as long as contamination is ruled out, whereas some investigators have taken an approach where scattered colonies were taken into account only if they were in a density of >5 colonies per cm² [38]. There has not been a consensus on this topic since its clinical significance has not been established. Therefore, confirmation with the reference agar dilution method is recommended when Etest or disk diffusion cannot be interpreted reliably.

Spectrum of activity

Fosfomycin is a broad-spectrum agent which has been shown to have excellent bactericidal activity against a range of gram-positive as well as gram-negative organisms, including drug-resistant varieties [40]. Since the epidemiology of antimicrobial resistance is changing rapidly, the studies published in the 21st century are referenced below.

Activity against Gram-positive organisms

Fosfomycin is broadly active against methicillin-susceptible and -resistant *S. aureus* (MRSA) with a modal MIC of about 1 µg/ml [41], but there may be a subset of highly resistant strains among MRSA [40]. It is also active against the majority of coagulase-negative *Staphylococcus* spp., but not as predictably as with *S. aureus* [41].

Fosfomycin is active *in vitro* against most *E. faecalis* strains and the majority of vancomycin-resistant *E. faecium* (VRE) strains with modal MICs of 32 to 64 µg/ml [36, 42, 43]. Unlike with *S. aureus*, high-level resistance in enterococci appears uncommon. Susceptibility of streptococcal species including *Streptococcus pneumoniae*, *Streptococcus pyogenes* and *Streptococcus agalactiae* are variable [36, 40, 41].

Activity against Gram-negative organisms

Fosfomycin has excellent activity against *E. coli*, the primary UTI pathogen, based on *in vitro* data available from various countries including the U.S. with the susceptibility to fosfomycin ranging between 98 and 100% [44–50]. Fosfomycin has shown good *in vitro* activity against *K. pneumoniae* with susceptibility rates between 70 and 85% and slightly higher susceptibility rates of 80 to 97% against *Proteus mirabilis* [44, 49]. Importantly, fosfomycin has excellent activity against extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae* [44, 49, 51]. For example, against ESBL-producing *E. coli*, fosfomycin had susceptibility rates of 86 to 100 % [49, 52, 53], which were generally higher than those seen with nitrofurantoin, ciprofloxacin or trimethoprim-sulfamethoxazole [54, 55]. However, in a study performed in Spain between 2005 and 2009, a strong correlation was observed between the use of fosfomycin among outpatients and fosfomycin resistance in ESBL-producing *E. coli* from UTI cases (from 4.4% in 2005 to 11.4% in 2009), suggesting that resistance rates may rise as more fosfomycin is used clinically.

In a review of 17 studies that evaluated the antimicrobial activity and clinical effectiveness of fosfomycin for infections caused by multidrug-resistant (MDR) *Enterobacteriaceae*, including ESBL-producing organisms, 11 studies reported that at least 90% of the isolates were susceptible to fosfomycin [56]. Using the CLSI susceptibility breakpoint of 64 µg/ml, the majority of ESBL-producing *E. coli* and *K. pneumoniae* isolates were susceptible to fosfomycin (97% and 81%, respectively).

There is a growing interest in potential use of fosfomycin for the treatment of infections caused by carbapenem-resistant *Enterobacteriaceae*, such as KPC-producing *K. pneumoniae*. In studies from the U.S., 86 to 93 % of KPC-producing *K. pneumoniae* isolates, including those non-susceptible to tigecycline or colistin, were susceptible to fosfomycin [57, 58], but only 67% of carbapenem-resistant *K. pneumoniae* were susceptible in a U.K. study [59]. In practice, fosfomycin is expected to be used in combination with other active agents in this scenario. Synergy has been observed between fosfomycin and meropenem in the majority of KPC-producing *K. pneumoniae* strains tested by the time-kill method [60].

Proteus spp., *Enterobacter* spp., *Citrobacter* spp., *Serratia marcescens* and *Salmonella enterica* are also generally susceptible to fosfomycin [41, 44]. For *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia*, the MICs cluster around 64 µg/ml, thus the interpretation will depend on the susceptibility breakpoint applied [36, 37, 40]. *Acinetobacter baumannii* and *Morganella morganii* are mostly resistant to fosfomycin [36, 40, 44], thus its use would only be considered in the context of combination therapy, especially for *A. baumannii*.

Pharmacokinetic properties of fosfomycin

Two fosfomycin salts are available for oral administration: fosfomycin tromethamine and fosfomycin calcium. Both salts are rapidly absorbed following oral administration, but the bioavailability is significantly better for fosfomycin tromethamine (40%) than fosfomycin calcium (12%) since fosfomycin calcium is inactivated by hydrolysis in the acidic gastric environment [61, 62]. Fosfomycin disodium is the only intravenous formulation available, marketed under different brand names and used extensively outside the U.S. This intravenous formulation is associated with a high sodium intake that could be a limitation in patients with heart failure or who are receiving hemodialysis [63].

Fosfomycin is a hydrophilic agent with negligible protein binding [64] and therefore is exclusively eliminated via glomerular filtration, with its clearance correlating well with the glomerular filtration rate [65]. After a single 3-gram dose, a maximum serum concentration ($C_{\max}$) of 22 to 32 $\mu\text{g/ml}$ is achieved in approximately 2 hours, with serum elimination half-life of 2.4 to 7.3 hours and area under the concentration-time curve of 145 to 228 $\mu\text{g/ml}\cdot\text{h}$ [66]. A high urine concentration (1,000 to 4,000 $\mu\text{g/ml}$) is achieved and remains over 100 $\mu\text{g/ml}$ for 30 to 48 hours, which is the pharmacokinetic basis for the single-dose oral regimen [67]. The volume of distribution (V_d) after an oral dose is 40 to 136 L depending on studies [64]. A 4-gram intravenous infusion achieves $C_{\max}$ of 200 to 250 $\mu\text{g/ml}$ and an 8-gram dose $C_{\max}$ of 260 to 450 $\mu\text{g/ml}$ [64]. In critically ill patients, the V_d can increase by as much as 50% due to increased capillary permeability, resulting in significantly lower maximum plasma concentrations during the dosing interval [68–70]. Hence, in critically ill patients, frequent and higher doses of fosfomycin over the first 24–48 hours may be beneficial in overcoming the increased V_d [69], but this needs to be balanced with variations in renal function, which is also common in the critical care settings [70].

The high penetration of fosfomycin leads to favorable distribution into many tissue types, including interstitial fluid of muscle [71] and soft tissue [72], infected lung tissue [73], heart valves [74], urinary bladder wall [75], prostate [76] and cerebral spinal fluid (CSF) [77]. However, it has highly variable abscess permeability, possibly necessitating multiple doses of fosfomycin to assist in exceeding the MICs of the target bacteria at the site of infection [78].

Renal impairment significantly decreases the excretion of fosfomycin since it is primarily eliminated via the urinary system. Therefore, doses should be reduced if the creatinine clearance is less than 50 ml/min [79]. Fosfomycin is eliminated by hemodialysis, but is largely retained between dialysis sessions, thus administration of 2 grams after hemodialysis and further administration after each subsequent hemodialysis session has been proposed for intravenous fosfomycin [80]. In patients receiving continuous renal replacement therapy (CRRT), peak and trough levels of fosfomycin are thought to be similar to plasma levels found in critically ill patients without renal replacement therapy or even healthy individuals [81]. After a 12-hour hemofiltration process, 77% of fosfomycin is expected to be removed, suggesting that its concentration is high enough at any time during CRRT to eradicate target pathogens. An intravenous dose of 8 grams every 12 hours is therefore recommended for patients on CRRT [81].

Adverse effects

Fosfomycin has a favorable safety profile in general, with the most common adverse event being mild gastrointestinal distress. The rate of these adverse events reported in the literature related to the use of oral fosfomycin vary between 2 and 6%, with the higher rates associated with patients treated with more than one doses [64, 82, 83]. A recent report indicated a high rate of mild hypokalemia (26%), suggesting that potassium monitoring may be prudent particularly when using prolonged courses of intravenous fosfomycin [82]. The effect on the intestinal flora after intake of a single 3-gram dose has not been well established. However, longer intravenous treatment (5 grams twice daily for 5 days) alters the intestinal flora significantly, mainly with a reduction of *Enterobacteriaceae* as noted in an older study conducted over two decades ago [84].

Drug interactions

Clinical data reporting drug interactions of fosfomycin with other agents are scarce. Nonetheless, metoclopramide, a gastrointestinal pro-motility agent, reduces the bioavailability of fosfomycin leading to lower serum concentration and urinary excretion of fosfomycin, whereas it has no effect on cimetidine [85]. Fosfomycin has been shown to ameliorate nephrotoxicity from nephrotoxic drugs in experimental models, including aminoglycosides [86], glycopeptides [87] and amphotericin B [88]. However, whether this observation translates to clinical benefits in reducing nephrotoxicity remains unknown.

Clinical uses and indications

The primary indication of oral fosfomycin is in the treatment of uncomplicated UTIs caused by common gram-negative organisms such as *E. coli* [89]. A large body of clinical trials data suggest the efficacy of the single-dose regimen to be similar to that of a single dose or 3 to 7-day courses of comparators including fluoroquinolones, trimethoprim-sulfamethoxazole, nitrofurantoin, amoxicillin-clavulanate and oral cephalosporins for the treatment of uncomplicated UTI [90]. More recently, a retrospective cohort study evaluating the use of oral fosfomycin among inpatients at a U.S. tertiary hospital between 2009 and 2013 found that, of the patients who received fosfomycin for rigorously defined UTI where the majority had *E. coli* as the causative organism, 74.8 to 89.9% had clinical success, with recurrent infection occurring in 4.3% of the patients [83]. Likewise, in a case-control study investigated risk factors of community-acquired infections caused by ESBL-producing *E. coli* in Spanish hospitals, the cure rate of patients with cystitis and treated with fosfomycin was 93%, with all the isolates being susceptible to fosfomycin [4].

For complicated UTIs, administration of oral fosfomycin 3 grams every 2 to 3 days has been suggested anecdotally based on its pharmacokinetics [85]. In fact, efficacy and safety data regarding multiple dose regimens of oral fosfomycin remain extremely scarce. A prospective, uncontrolled, open-label study conducted in China evaluated the clinical and microbiological efficacy and safety of three 3-gram doses of fosfomycin tromethamine administered orally every 48 hours to treat complicated and uncomplicated lower UTIs [91]. The clinical efficacy rates at day 15 for acute uncomplicated cystitis, recurrent lower urinary

tract infection and complicated lower urinary tract infection were 95%, 77% and 63%, respectively, and the microbiological efficacy rates were 98%, 94% and 84%, respectively. In a case series of complicated and uncomplicated UTIs caused by MDR organisms (including ESBL and KPC-producing *K. pneumoniae* and *E. coli*, *P. aeruginosa* and VRE), patients received an average of 2.9 doses of fosfomycin, resulting in a microbiological cure rate of 59% despite 86% *in vitro* susceptibility of the causative organisms [43].

Fosfomycin has reasonable intraprostatic concentrations following a 3-gram oral dose, making it an option for perioperative prophylaxis in prostate resection procedures when compared to the fluoroquinolones [92, 93] and even possibly for the treatment of prostatitis caused by MDR organisms [76, 94]. Notably, once daily dosing was well tolerated while twice a day dosing was associated with fecal urgency and diarrhea in a patient with prostatitis [94].

UTIs are common during pregnancy due to hormonal and anatomic-physiological changes that facilitate the growth and dissemination of bacteria in the maternal urinary tract [95]. Although fosfomycin crosses the placental barrier, it appears to be safe for use during pregnancy [96] and is well tolerated [97]. A single dose of fosfomycin tromethamine has been shown to be as efficacious as cefuroxime or amoxicillin-clavulanate in randomized trials of uncomplicated UTI among pregnant women [98, 99]. Oral fosfomycin has also been shown to be effective in the prophylaxis of recurrent UTIs in a randomized trial comparing oral fosfomycin given every 10 days for 6 months when followed for a period of 6 months (0.14 infections/patient year vs 2.97 infections/patient year in the placebo arm) [100].

In serious systemic infections other than uncomplicated UTI, intravenous fosfomycin is given at a dosage of 2 to 24 g a day divided in 3 to 4 doses, mostly in combination with other active agents [64, 101]. Potential use of intravenous fosfomycin for the treatment of infections due to MRSA, VRE, and MDR gram-negative bacteria in combination with other agents has gained substantial interest due to its unique mechanism of action and potential protective effect against nephrotoxicity from aminoglycosides or colistin [63]. Intravenous fosfomycin has also been used to treat skin and soft tissue infections [102] as well as intraocular infections given the excellent diffusion of fosfomycin into the aqueous humor [103].

A 'real practice' multicenter, open-label, phase III randomized controlled trial coined FOREST (Fosfomycin versus meropenem in bacteraemic urinary tract infections caused by extended-spectrum β -lactamase-producing *Escherichia coli*) is ongoing in Spain [104]. The main objective of the study is to demonstrate the clinical non-inferiority of intravenous fosfomycin against meropenem for the treatment of bacteremic UTI caused by ESBL-producing *E. coli*. It is designed to compare the clinical and microbiological efficacy and safety of intravenous fosfomycin (4 g every 6 hours) and meropenem (1 g every 8 hours) as definitive therapy. The study is expected to provide high-quality clinical data on the feasibility of using intravenous fosfomycin for systemic ESBL-producing *E. coli* infections.

***In vitro* and clinical data on combination therapy for MDR infections**

Given the unique mechanism of action of fosfomycin, its use in combination with other agents is gaining popularity with many *in vitro* studies supporting the use, especially against MDR organisms in adults (see below) and even children [105]. Various combinations have been tested for *in vitro* synergy including fosfomycin-linezolid for treatment of MRSA infections [106], fosfomycin-amoxicillin and fosfomycin-daptomycin against VRE [107], fosfomycin-ceftriaxone against MDR *Neisseria gonorrhoeae* [108], fosfomycin-imipenem against MDR *Pseudomonas aeruginosa* [109], fosfomycin-colistin against XDR *Acinetobacter baumannii* [110] and amikacin-fosfomycin combination as a nebulized formulation against ventilator-associated pneumonia [111]. Promising results have also been shown in triple drug regimens with fosfomycin and other agents such as daptomycin, colistin, meropenem, rifampin, telavancin, tigecycline and vancomycin against VIM- and NDM-producing *K. pneumoniae* by time-kill experiments [112].

A prospective evaluation to assess the safety and efficacy of fosfomycin as an adjunct to the therapy of life-threatening infections caused by carbapenem-resistant *K. pneumoniae* from Greece showed that all 11 patients had generally good clinical outcome of infection with 2 in-hospital deaths when fosfomycin was administered intravenously (2 to 4 g every 6 h) for the treatment of hospital-acquired infections caused by this organism [63]. The partner agents were colistin (6), gentamicin (3) and piperacillin-tazobactam (1). Another retrospective study of trauma patients in Italy mirrored these results [113]. Using tigecycline as the backbone drug to treat KPC-producing *K. pneumoniae* infections with either colistin or gentamicin as the second drug, fosfomycin was given as the third drug in 13 of the 26 episodes. Overall, a favorable response to therapy was documented for 92% of the infectious episodes. In a case report from the U.S. where only oral fosfomycin is approved, bacteremia caused by KPC-producing *K. pneumoniae* in a bone marrow transplant patient, which was refractory to meropenem, tigecycline, amikacin and colistin, finally cleared with a combination of doxycycline, meropenem and high dose of oral fosfomycin (9 g every 8 hours) [114]. There is also a report of intravenous fosfomycin use in a U.S. hospital, where refractory bacteremia due to colistin-resistant carbapenem-resistant *K. pneumoniae* was treated with a combination of meropenem, amikacin, colistin, rifampin and intravenous fosfomycin imported from Europe, which led to resolution of bacteremia [115]. However, development of fosfomycin resistance during therapy has also been reported even in combination therapy, which may become a limiting factor in the use of fosfomycin in this context [116].

For methicillin-resistant *S. aureus* (MRSA), 16 patients with MRSA bacteremia or endocarditis who had failed treatment with vancomycin and/or daptomycin were treated with a combination of intravenous fosfomycin (2 g every 6 hours) and imipenem for a median of 28 days [117]. All patients achieved negative blood cultures within 72 hours, and 11 were cured at the test-of-cure visit. To confirm this promising finding, a multicenter, open-label randomized study is planned in Spain, where patients with MRSA bacteremia will be assigned to daptomycin alone or daptomycin plus fosfomycin (2 g every 6 hours) and followed for 6 weeks. The study is powered to demonstrate superiority of the latter approach with 20% difference in the cure rates.

Conclusions

Fosfomycin has drawn significant attention in recent years due to its broad-spectrum activity that includes MDR gram-negative organisms such as ESBL-producing *E. coli* and, to some extent, KPC-producing *K. pneumoniae*. Its clinical efficacy for uncomplicated UTI is excellent, whereas clinical data on the treatment of more invasive infections are just beginning to emerge, both as stand-alone therapy and in combination therapy. Its potential use as an adjunct for the treatment of invasive MRSA infection is another application that appears promising. At the same time, emergence and spread of resistance, including transferable resistance, in some corners of the world is concerning and requires close monitoring. Overall, fosfomycin is expected to remain and be further harnessed as a critical component of the treatment armamentarium against MDR pathogens in the coming years.

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Figure 1.
Structure of fosfomycin tromethamine

Table 1

Mechanisms of fosfomycin resistance.

Mechanism	Protein involved	Action
Reduced permeability	GlpT	Modifications or reduced expression of glycerol-3-phosphate transporter
	UhpT	Modifications or reduced expression of hexose phosphate transporter
Target modification	MurA	Modifications or overexpression of UDP-N-acetylglucosamine 1-carboxyvinyltransferase
Inactivation of drug	FosA	Mn ²⁺ -dependent glutathione-S-transferase
	FosB	Mn ²⁺ /Mg ²⁺ -dependent bacillithiol-S-transferase
	FosX	Mn ²⁺ -dependent epoxide hydrolase
	FosC (FomA)	Mg ²⁺ /ATP-dependent phosphorylation of fosfomycin

Table 2

Susceptibility breakpoints for fosfomycin.

	MIC				Zone diameter			Notes
	Susceptible	Intermediate	Resistant		Susceptible	Intermediate	Resistant	
CLSI	64 µg/ml	128 µg/ml	256 µg/ml		16 mm	13–15 mm	12 mm	<i>E. coli</i> and <i>E. faecalis</i> urinary isolates (oral only)
EUCAST	32 µg/ml	-	>32 µg/ml		-	-	-	<i>Enterobacteriaceae</i> (oral and intravenous) and <i>Staphylococcus</i> spp. (intravenous only)

The medium should be supplemented with 25 µg/ml of glucose-6-phosphate for dilution methods.
The disk contains 200 µg of fosfomycin and 50 µg of glucose-6-phosphate.