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Review

Resistance to fosfomycin: Mechanisms, Frequency and Clinical Consequences

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ABSTRACT

Fosfomycin has been used for the treatment of infections due to susceptible and multidrug-resistant (MDR) bacteria. It inhibits bacterial cell wall synthesis through a unique mechanism of action at a step prior to that inhibited by β-lactams. Fosfomycin enters the bacterium through membrane channels/transporters and inhibits MurA, which initiates peptidoglycan (PG) biosynthesis of the bacterial cell wall. Several bacteria display inherent resistance to fosfomycin mainly through MurA mutations. Acquired resistance involves, in order of decreasing frequency, modifications of membrane transporters that prevent fosfomycin from entering the bacterial cell, acquisition of plasmid-encoded genes that inactivate fosfomycin, and MurA mutations. Fosfomycin resistance develops readily in vitro but less so in vivo. Mutation frequency is higher among *Pseudomonas aeruginosa* and *Klebsiella* spp. compared with *Escherichia coli* and is associated with fosfomycin concentration. Mutations in cAMP regulators, fosfomycin transporters and MurA seem to be associated with higher biological cost in Enterobacteriaceae but not in *Pseudomonas* spp. The contribution of fosfomycin inactivating enzymes in emergence and spread of fosfomycin resistance currently seems low-to-moderate, but their presence in transferable plasmids may potentially provide the best means for the spread of fosfomycin resistance in the future. Their co-existence with genes conferring resistance to other antibiotic classes may increase the emergence of MDR strains. Although susceptibility rates vary, rates seem to increase in settings with higher fosfomycin use and among multidrug-resistant pathogens.

1. Introduction

Fosfomycin was discovered in 1969 and is a low molecular mass (138 Da) derivative of a phosphoric acid isolated from cultures of Streptomyces spp. (*Streptomyces fradiae, Streptomyces viridochromogenes*, and *Streptomyces wedomorensis*) [1–3]. It is also produced in a biosynthetic process involving a unique combination of carbon and phosphorous [1,3]. The structure of fosfomycin has two key features: an epoxide group, which is essential for its biological activity, and a phosphonic acid moiety.

Fosfomycin remains one of the first-line agents for the treatment of acute uncomplicated urinary tract infections (UTIs) mainly caused by *Escherichia coli* (+/- extended spectrum β-lactamase [ESBL]), *Klebsiella* spp., *Proteus mirabilis, Staphylococcus saprophyticus, Enterococcus* spp., and *Streptococcus agalactiae* [3,4]. Intravenous fosfomycin is also approved in several European countries for the treatment of infections outside the urinary tract [4]. There is a global interest to further investigate fosfomycin as monotherapy and in combination with other antimicrobial agents for the treatment of serious systemic infections due to multidrug-resistant (MDR) Gram-negative bacteria [5–8]. Hence, mechanisms of resistance, potential for development of resistance, frequency of resistant isolates, and possible clinical consequences are of major importance. These issues will be summarized in this review.

2. Mechanism of action

Fosfomycin invades the bacterium through two different membrane transportation systems: L-alpha glycerol-3-phosphate and

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Table 1
Mechanisms of fosfomycin resistance.

Mechanism of resistance	Bacterium	No. of reference
Inherent resistance		
Cysteine to Aspartate change in the active site of MurA	*Mycobacterium tuberculosis* *Chlamydia trachomatis* *Vibrio fischeri*	[12–14, 82]
Existence of recycling pathways in peptidoglycan synthesis that MurA does not participate	*Pseudomonas putida* *Pseudomonas aeruginosa* *Chlamydia trachomatis*	[12,15,16]
Acquired resistance		
Mutations in the structure of glpT and uhpT	*Escherichia coli*	[19,20, 83]
Modification in the uhpA gene → decreased expression of uhpT	*Escherichia coli*	[20]
Alterations in the ptsI & cyaA genes → reduction of intracellular levels of cAMP	*Escherichia coli*	[20–22]
New amino acid substitutions in MurA (Asp369Asn & Leu370Ile)	*Escherichia coli*	[19]
Overexpression of MurA & alterations lead to low affinity between enolpyruvyl transferase and fosfomycin	*Escherichia coli*	[25, 84]
FosA, FosA2, FosA3, FosA4, FosA5, FosA6 (Plasmid-borne resistance)	Enterobacteriaceae	[27,29,30,32,53]
FosB (Plasmid-borne resistance)	*Staphylococcus* spp. *Enterococcus* spp. *Bacillus subtilis*	[35,38,39]
FosX (Plasmid-borne resistance)	*Listeria monocytogenes*	[42, 85]
FosC (Plasmid-borne resistance)	*Pseudomonas syringae*	[86]
FomA & FomB (kinases)	*Streptomyces* spp.	[44]

the glucose-6-phosphate transporter (G6P) (GlpT and UhpT, respectively) [1]. The chemical structure of fosfomycin imitates both glycerol-3-phosphate and G6P, which are normally transferred trough GlpT and UhpT and induce their expression [8]. Cyclic adenosine monophosphate (cAMP) is also essential for the expression of the genes of both transportation systems [1].

The bacterial activity of fosfomycin involves interfering with the initiating reaction in the biosynthesis of peptidoglycan (PG), the main constituent of the bacterial cell wall. Specifically, fosfomycin inhibits the enzyme UDP-*N*-acetylglucosamine enolpyruvyl transferase (or MurA), which takes part in the transportation of the enolpyruvyl moiety of phosphoenolpyruvate (PEP) to the 3'-hydroxyl group of UDP-*N*-acetylglucosamine (UNAG) that is required for the biosynthesis of PG [9,10]. Fosfomycin forms a covalent adduct with the thiol group of a cysteine and inactivates the active side of MurA. Consequently, UDP N-acetylmuramic acid – the precursor of PG – is not formed, leading to the loss of PG layer integrity, cell lysis and death [1,9]. Besides its direct antimicrobial activity, fosfomycin exerts immunomodulating action by altering the levels of TNF-a, interleukins, and leukotrienes, and modulating the function of neutrophils and T- and B-lymphocytes; it also reduces bacterial adherence to the epithelia of the respiratory and urinary tracts [1,11,12].

3. Mechanisms of resistance

Fosfomycin remains active against a significant proportion of Gram-negative and Gram-positive bacteria. MDR pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococci* (VRE), and ESBL- and carbapenemase-producing Enterobacteriaceae are also susceptible to fosfomycin [1,11] (Table 1). However, several resistance mechanisms have been described. Specifically, mechanisms that constitute bacteria inherently resistant to fosfomycin have been identified, including *Chlamydia* spp., *Vibrio fischeri*, and *Mycobacterium tuberculosis* that continue to grow in vitro even under high concentrations of the drug [12–14]. In addition, acquired, potentially transferable resistance mechanisms are increasingly reported. Heteroresistant populations have also been described.

3.1. Inherent resistance

Regarding the mechanisms of inherent resistance, mutations in the *MurA* gene confer resistance to fosfomycin due to a structural replacement of cysteine with aspartate in the active site of MurA, which prevents fosfomycin binding to MurA. Similarly, *M. tuberculosis* isolates became susceptible following replacement of aspartate by cysteine in position 117 of MurA.

Chlamydial MurA is suggested to have limited enzymatic participation in the chlamydial life cycle, i.e. during the conversion of elementary bodies (EBs) to reticulate bodies (RBs) and at the beginning of cell differentiation. During these stages, the pH of the inclusion provides an optimal MurA activity that diminishes with the subsequent environmental changes due to cell development [12].

Recently, several studies confirmed the existence of recycling pathways for PG synthesis, instead of its de novo biosynthesis, in *Pseudomonas putida* and *Pseudomonas aeruginosa* [15,16]. Specifically, a metabolic pathway consisting of an anomeric cell wall amino-sugar kinase (AmgK) and an uridylyl transferase (MurU) was described [15]. Together, these change N-acetylMurAmic acids (MurNAc) into uridine diphosphate (UDP)-MurNAc, using MurNAc a-1-phosphate, thus bypassing the de novo synthesis of UDP-MurNAc, which is the target for fosfomycin action [15]. Recycling of PG by chlamydia during the later phases of the development cycle has also been postulated; this would render the chlamydial MurA less essential during the process of changing into more advanced forms [12].

An interesting phenomenon that renders *Listeria monocytogenes* resistant to fosfomycin in vitro but susceptible in vivo has been described. The bacterium cannot uptake the antibiotic in vitro, but in vivo or during infection it expresses the glucose-6-phosphate permease Hpt that accommodates fosfomycin uptake, thus rendering *L. monocytogenes* susceptible to fosfomycin [17].

A new gene called *abrp* conferring a 4-fold decreased susceptibility to fosfomycin in *A. baumannii* has recently been described; decreased susceptibility to tetracyclines, tigecycline and chloramphenicol was also confirmed [18]. The gene was located in the chromosome and was involved in modification of membrane permeability. The *abrp* gene was found to be essential for bacterial growth; deletion of the gene reduced growth rate by 17%.

3.2. Acquired resistance – fosfomycin transportation

Bacteria may develop resistance to fosfomycin following chromosomal mutations in the structural genes that encode the GlpT and UhpT membrane transporters, which transport glycerol and other carbohydrates required for metabolic functions and virulence

of bacteria like *E. coli*. Fosfomycin uses the same transporters to facilitate bacterial entry. Thus, these mutations block fosfomycin cell penetration [19,20]. The absence of the entire portion of the *uhp* region, such as *uhpA*, might reduce the effectiveness of the bacterial transportation systems [19]. The *uhpA* gene encodes a response regulator protein required for transcriptional activation of the *uhpT* promoter. Thus, modifications in the *uhpA* gene results in lower expression of *uhpT*. Furthermore, alterations in the *ptsI* and *cyaA* genes lead to reduction of intracellular levels of cAMP, which in turn lowers the expression of GlpT and UhpT transporters and consequently fosfomycin uptake by the bacteria [20–22].

Mutations in the *ptsI* and *cyaA* genes can also decrease biosynthesis of bacterial pilus (which helps them to survive and multiply in the urinary bladder). Decreased pilus biosynthesis reduces adherence to uroepithelial cells [21–23]. These data could explain the low virulence of fosfomycin-resistant bacteria in urinary infections [23,24].

3.3. *Acquired resistance* – murA *related*

A mutation has been described in which aspartate substitutes for cysteine in position 115 of the *E. coli* MurA and renders susceptible isolates highly resistant to fosfomycin [25]. Other amino acid substitutions in MurA (Asp369Asn and Leu370Ile) have also been associated with fosfomycin resistance [19]. The enhanced transcription of *murA* in the presence of specific substances that enhance bacterial growth results in fosfomycin resistance with a lower fitness cost compared with permeability mutants [25,26]. Clinical isolates involving this mechanism of resistance have not been reported.

3.4. *Acquired resistance – antibiotic modification*

Resistance to fosfomycin develops through the acquisition of plasmid-encoded genes that inactivate the antibiotic. The plasmid–mediated Fos enzymes belong to the glyoxalase superfamily [3]. This mechanism was first described for the metalloenzyme glutathione S-transferase encoded by *FosA* [27]; this enzyme uses Mn^{+2} and K^{+} as cofactors. Glutathione S-transferase inactivates fosfomycin by opening the antibiotic epoxide group and adding the sulphydryl group of the cysteine of tripeptide glutathione (GSH) to C1 of the epoxide ring of fosfomycin [27–29]. The *FosA* gene is mostly found in Enterobacteriaceae, *Pseudomonas* spp. and *Acinetobacter* spp. [27]. New subtypes with accurate description of the *FosA* structure have been identified: *FosA2, FosA3, FosA5*, and *FosA6* [21,30,31]. The *FosA2* gene has 95% amino acid identity to *FosA* [32]; other *FosA* genes were similar. Thus, the *FosA5* gene encodes a 139-amino-acid protein that shares 69-80% of its structure with proteins encoded by *FosA, FosA2, FosA3* and *FosA4* genes [30]. Concurrence of these genes, in either the same or a conjugate plasmid, with several other genes conferring resistance to β-lactams, aminoglycosides, fluoroquinolones, tetracyclines and sulfonamides has been described [21,33,34].

The second enzyme of the glyoxalase superfamily conferring resistance to fosfomycin is FosB [3]. Although the FosB amino acid sequence has 38% identity to FosA, it differs from FosA in that it is a Mg^{+2}-dependent enzyme and uses l-cysteine (l-Cys) as the physiologic thiol donor [35]. It catalyzes the nucleophilic addition of either l-Cys or bacillithiol (BSH) to fosfomycin, resulting in a modified compound with no bactericidal properties [21,35,36]. Expression of *FosB* requires the extracytoplasmic sigma factor, SigW [35], a regulator with a prominent role in providing inducible resistance to antimicrobial compounds [37]. The currently available data indicate that the *FosB* gene is mainly expressed in Gram-positive bacteria, and is either plasmid- (in *Staphylococcus* spp. and *Enterococcus* spp.) or chromosomally- (in *Bacillus subtilis*) encoded [35,38,39]. This gene was found in the same transposon of conjugative plasmids as the *vanA* gene in 10 of 18 VRE [38]. In addition, *FosB* was identified in 46% of fosfomycin-resistant *S. aureus* isolates in an older study [39]. However, *FosB* probably has a minor role in fosfomycin resistance among MRSA strains. In contrast, the presence of *FosA* and mutations in *MurA, glpT*, and *uhpT* genes might have a major role in conferring resistance to fosfomycin [35,39].

FosX is a hydrolase sharing 30-35% sequence identity with FosA and FosB [40]. It is an Mn^{+2}-dependent enzyme encoded by chromosomal genes of *L. monocytogenes*. Homologues of the *FosX* gene have been found in the genome of *Mesorhizobium loti, Clostridium botulinum* and *Brucella melitensis* [41]. FosX renders fosfomycin inactive by adding water to the C1 position of fosfomycin and opening its epoxide ring, like other Fos enzymes [42].

Lastly, kinases found in fosfomycin-producing bacteria, such as *Streptomyces wedmorensis* and *Streptomyces fradiae*, have been shown to protect against the bactericidal activity of fosfomycin. These enzymes are encoded by *fomA* and *fomB* genes and inactivate fosfomycin by phosphorylation [43]. The *fomA* gene catalyzes phosphorylation of the fosfomycin phosphate group to fosfomycin monophosphate and *fomB* converts fosfomycin monophosphate to fosfomycin diphosphate. Both reactions are catalyzed by ATP and Mg^{+2}, similar to Mg-ATP-binding sites of eukaryotic kinases [21,43,44]. Interestingly, *fomA* has 25.8% identity to the *fosC* gene produced by *Pseudomonas syringae*. FomC exhibits similar activity by converting fosfomycin to fosfomycin monophosphate [43].

3.5. *Heteroresistance*

Heteroresistance describes a phenomenon where small subpopulations of seemingly susceptible bacteria can grow after exposure to antibiotic (obviously due to resistance to the antibiotic).

Heteroresistance to fosfomycin has been described in 10 of 11 *Streptococcus pneumoniae* strains. When *MurA* was deleted, heteroresistance was abolished. The isolate that did not display heteroresistance had an amino acid substitution in MurA (Ala364Thr) [45]. To evaluate if this single substitution is associated with the absence of heteroresistance, this mutation was introduced into a non-heteroresistant strain: the phenotype did not change. As there is no other structural difference in MurA between the heteroresistant and susceptible strains, heteroresistance was concluded to be probably multifactorial [45]. Heteroresistance to fosfomycin was also described in MDR and non-MDR *P. aeruginosa* clinical isolates from Australian hospitals. Baseline population analysis profiles indicated heteroresistance in all tested isolates. In time-kill studies, treatment with fosfomycin at any concentration resulted in complete replacement of fosfomycin-susceptible by fosfomycin-resistant colonies [46].

4. Frequency of fosfomycin resistance

Early in vitro reports indicated that fosfomycin exhibited considerable antimicrobial activity against Gram-negative and Gram-positive urinary isolates, including Enterobacteriaceae, *staphylococci* (including both methicillin-susceptible *S. aureus* [MSSA] and MRSA) and *E. faecalis*, but not against *P. aeruginosa* and *Acinetobacter baumannii* [47]. Reviews reported that fosfomycin exhibited cumulative susceptibility rates of 87.9% against MRSA and 87.2% against penicillin-non-susceptible pneumococcal isolates. Activity against VRE was much lower (30.3%) and more variable [48]. Fosfomycin was found to be considerably active against MDR Enterobacteriaceae isolates (96.8% of ESBL-producing *E. coli* and 81.3% of ESBL-producing *K. pneumoniae* isolates) [49]. However, fosfomycin was active against 30.2% of MDR *P. aeruginosa* isolates, but only against 3.5% of MDR *A. baumannii* and none of the 31 MDR *Burkholderia* species isolates [50].

The susceptibility of contemporary Gram-positive and Gram-negative bacteria to fosfomycin was summarized in a recent review of studies published between 2010 and 2015 [11]. Fosfomycin susceptibility generally remained relatively high but varied in individual bacteria and by geographical region. Declining activity was observed with increasing β-lactam resistance patterns but not with vancomycin resistance. In general, *S. aureus* and *E. coli* were susceptible to fosfomycin with low minimum inhibitory concentrations (MICs). Fosfomycin activity ranged between 33.2% and 100% against *S aureus* (including MRSA strains); from 30% to 100% for *Enterococcus* spp.; from 81% to 100% for ESBL-producing *E. coli*; from 15% to 100% for ESBL-producing *K. pneumoniae* and from 39.2% to 100% for carbapenem-resistant *K. pneumonia*. Susceptibility of ESBL-producing *E. coli* and *K. pneumoniae* isolates was higher in developed than in developing countries, but there was no difference between countries in KPC-producing *K. pneumoniae* strains [11]. Studies published after this review provided further evidence of fosfomycin activity against a variety of bacteria in various parts of the globe [51–56].

5. Factors influencing resistance mutation frequency

The frequency of mutations resulting in fosfomycin resistance in Gram-negative bacteria has been evaluated in several studies [21]. Mutants that are resistant to fosfomycin generally develop rapidly in vitro [24]. This occurs at higher frequency for strains of *P. aeruginosa* or *K. pneumoniae* compared with *E. coli* [57,58]. In addition, fosfomycin-resistant mutants of *E. coli* strains appeared more frequently than rifampin-resistant mutants; similarly, fosfomycin-resistant mutants of *P. aeruginosa* emerged more frequently than for tobramycin but not for imipenem [59]. Resistance to fosfomycin can develop through single-step mutations in *E. coli* hypermutable strains [58]. Hypermutable *E. coli* or *P. aeruginosa* strains have a 10- to 100-fold higher frequency of developing fosfomycin-resistant mutants [59–61]. However, such strains are also more likely to produce mutations that do not facilitate their longevity [62].

Resistance develops at a lower frequency with higher fosfomycin concentrations [57]. Emergence of fosfomycin-resistant mutants for different bacteria in vitro at three different fosfomycin concentrations (250, 1000 and 2000 mg/L) was inversely associated with fosfomycin concentration [57]. Although no fosfomycin-resistant mutants were seen with 2000 mg/L fosfomycin, resistant mutants were observed with 250 mg/L fosfomycin for all *K. pneumoniae* and *P. aeruginosa* strains, and three of five *Proteus* spp. strains, but none of the three *E. coli* strains [57]. In a simulated in vitro model of bacterial cystitis, four *E. coli* strains with different susceptibility profiles were tested at different fosfomycin concentrations. Resistant mutants were observed with fosfomycin concentrations of 50 and 250 mg/L, even for the two fully susceptible strains. In contrast, no resistant mutants were observed when the peak fosfomycin concentration was 2500 mg/L [63]. These findings are clinically significant in view of studies showing high interindividual variability and reduced time > MIC, $AUC_{0\text{-}7days}$/MIC, and C_{max}/MIC values in urinary concentrations of healthy women receiving 3 g fosfomycin trometamol [64].

Similar issues may arise in other body sites, where concentrations of fosfomycin are not as high as in urine. Although reported peak serum concentrations were variably high (up to 600 mg/L) after intravenous infusion [65], the respective concentrations in relevant tissues were significantly lower. Site-to-serum concentration ratios can be 0.39–0.69 for muscle, 0.32–0.54 for lung tissue, 0.39–0.49 for subcutaneous tissue, 0.23–0.26 for cortical bone, and 0.17–0.20 for cerebrospinal fluid [21,65]. The clinical significance of the variable penetration of fosfomycin in different body sites in terms of resistance development requires further study. Exposure of pathogens to different concentrations of antibiotics, particularly those close to their MIC, may promote different levels of resistance [66,67].

6. Clinical significance of fosfomycin resistance

Historically, mutations in nutrient transporters were the mechanisms of resistance most frequently observed in vitro; Table 2 shows this remains the most common mechanism of resistance in contemporary studies [19,51,68–75]. Mutations in *MurA* gene and in *ptsI* and *cyaA* genes are relatively uncommon in clinical isolates. The importance of *MurA* in PG synthesis and of *ptsI* and *cyaA* in regulation of cAMP levels indicates that such mutations may be associated with high biological cost. Therefore, such mutations are not expected to be clinically significant unless the bacteria develop compensatory mechanisms [22]. Thus, although in vitro development of resistance in *E. coli* strains following mutations in *glpT, uhpA/T, ptsI*, and *cyaA* was highly probable, mutations in *ptsI* and *cyaA* were not observed in clinical isolates [22]. All mutations developing in vitro resulted in decreased bacterial growth rate of affected pathogens (either in urine or in laboratory media and in the presence or absence of fosfomycin) compared with that of susceptible isolates [22]. Further evidence supporting greater biological cost among fosfomycin-resistant strains comes from an *E. coli* murine infection model showing lower virulence among resistant compared with susceptible strains [76]. The two strains in this study seemed to carry *glpT* and *ptsI* mutations.

Decreased bacterial growth has been shown not only for *E. coli* strains but also for *K. pneumoniae* and *P. mirabilis* [23,77]. Furthermore, studies have shown that fosfomycin-resistant mutants have decreased capacity to adhere to uroepithelial cells [23,77], which indicates that mutations may be associated with decreased virulence in urinary tract infections. However, this does not seem to be the case for *S. aureus* and *P. aeruginosa*, in which resistance to fosfomycin does not seem to be associated with any fitness cost compared with wild-type strains [59,78].

Although the contribution of fosfomycin-inactivating enzymes in emergence and spread of fosfomycin resistance currently seems low-to-moderate, their presence in transferable plasmids may potentially provide the best means for the spread of fosfomycin resistance in the future. Several studies indicate outbreaks caused by such bacteria have occurred, and dissemination of these clones may render inactivating enzymes the predominant mechanism of fosfomycin resistance [51,68,69,78]. In addition, their co-existence with other genes conferring resistance to other antibiotic classes, including β-lactams, fluoroquinolones, tetracyclines, macrolides, sulfonamides and aminoglycosides, worsens the emergence of MDR strains. Co-occurrence in plasmids with *bla*CTX-M, *bla*CMY, *bla*TEM, *bla*SHV, *bla*SFO-1, *bla*AmpC, *bla*NDM, *bla*KPC, *bla*OXA, *gyrA, parC, parE, sul1, sul2, strA, strB, aac*(6=)*-Ib, aadA5, aphA6, tetA*(A), *mphA, floR, dfrA7, rmtB*, and *merA* genes has been reported [1]. Emerging resistance to fosfomycin during treatment and an increase in β-lactam MICs following treatment with these agents was reported in three KPC *K. pneumoniae* isolates in a Greek hospital. The resistant bacteria were considered mutants of the pre-treatment bacteria [79].

Fosfomycin has not been widely used compared with other antibiotics; thus, fosfomycin resistance has not been observed in studies that did not account for fosfomycin consumption [21]. A meta-analysis showed that single-dose fosfomycin for cystitis treatment was not associated with resistance [49]. A second meta-analysis of 128 studies estimated the pooled probability for development of resistance during treatment for bacteremia, urinary tract, respiratory tract, bone and joint, and central nervous system infections was 3.4% (95% CI 1.8-5.1%) [80]. Resistance developed mainly in strains of *P. aeruginosa, Klebsiella* spp., *Proteus* spp. *and Enterobacter* spp. However, a 50% increase in fosfomycin

Table 2
Prevalence of resistance mechanisms to fosfomycin in contemporary isolates from clinical samples.

Author	Location	Microorganisms (N)	Resistance/ non-susceptibility to fosfomycin	MurA n/N (%)	Transporters n/N (%)	fos group n/N (%)	Remarks
White et al. 2017 [68]	USA	KPC-producing *Enterobacter* (19)	26% CLSI 42% EUCAST	NR	NR	fosA 8/19 (42.1)	4/8 of *fos*A producers were susceptible to fosfomycin
Bi et al. 2017 [69]	China	ESBL *E. coli* (356)	6.7% (CLSI)	3/24 (12.5)	3/24 (12.5)	fosA3 20/24 (83.3)	14/20 *fos*A3 in transferable plasmids
Ohkosi et al. 2017 [70]	Japan	*E. coli* (211)	0.4% (CLSI)	None	9/10 (90)*	none	reduction of *uhpT* expression was responsible for the reduced susceptibility
Lu et al. 2016 [71]	Taiwan	ESBL *K. pneumoniae* (108)	27.8% (CLSI)	21/30 (70)	29/30 (97)	none	NA
Fu et al. 2016 [72]	China	MRSA (96)	69.8% (EUCAST)	2/67 (7.3)	60/67 (89.6)	fosB 9/67 (13.4)	5 and 29 fosfomycin susceptible isolates carried *mur*A and transporter mutations, respectively
Tseng et al. 2015 [73]	Taiwan	ESBL *E. coli* (145)**	9% (CLSI)	3/13 (23.1)	9/13 (69.2)	fosA3 4/13 (30.8)	NA
Jiang et al. 2015 [74]	China	KPC and ESBL *K. pneumoniae* (278 and 80)	60.8% and 12.5% (EUCAST)	Not done	Not done	fosA3 93/94 (98.9) and 10/10 (100)	Clonal dissemination
Li et al. 2015	China	*E. coli* (1109)***	7.8% (CLSI)	4/86 (4.7)	7/86 (8.1)	fosA3 69/86 (80.2)	29/69 *fos*A3 in transferable plasmids
Takahata et al. 2010 [19]	Japan	*E. coli* (6)	100% (CLSI)	2/6 (33)	4/6 (67)	NA	
Oteo et al. 2009 [75]	Spain	ESBL *E. coli* (26)	100% (NA)	0/4 (0)	2/4	NA	NA

* Ten strains (4.7%) had reduced susceptibility to fosfomycin (MIC ≥ 8 mg/L).
** 22 strains were isolated from pigs; fosfomycin resistance was higher in these isolates (23% vs. 6.6%).
*** 67.2% ESBL-positive strains.
Abbreviations: CLSI, Clinical and Laboratory Standards Institute; ESBL, extended spectrum β-lactamase; EUCAST, European Center for Antibiotic Susceptibility Testing; KPC, *K. pneumoniae* carbapenemase; MRSA, methicillin resistant *S. aureus*; NR, not reported; NA, not applicable.

use resulted in an increase of fosfomycin-resistant, ESBL-producing *E. coli* strains (from 2.2% in 2003 to 21.7% in 2008; $P<0.001$) as well as among all isolates (from 1.6% in 2003 to 3.8% in 2008; $P<0.001$) in a study that evaluated 17 602 urinary tract infections [75]. This finding was confirmed in a second 7-year-long study [81]. Other studies reported development of resistance during treatment in 0-6.7% of cases, with *P. aeruginosa* the leading strains developing resistance (7-20%) [21].

7. Conclusion

Fosfomycin is an old antibiotic that is being reconsidered for the treatment of lower urinary tract and other systemic infections caused by Gram-positive and Gram-negative bacteria. Its re-emergence as an antibiotic of interest is due to the global increasing resistance of several bacteria to numerous antimicrobials. There are several mechanisms of resistance to fosfomycin; the contribution of fosfomycin susceptibility rates varies in an evolving environment. Each mechanism may provide advantages to the mutant bacteria, but may also be associated with biological cost (reduced growth rate, lower virulence). There is a discrepancy between the data from in vitro and clinical studies regarding development of resistance. This may be because of the complex biological phenomenon of infection, in which there is interplay between bacteria, antibiotics, site of infection, presence of foreign materials and function of the immune system. Ultimately, the current fosfomycin activity seems to be more than satisfactory and justifies its use as monotherapy or in combination with other antibiotics for treatment of infections caused by susceptible and multidrug-resistant bacteria.

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Conflict of interest

None

Ethical approval

None

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