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Fosfomycin

Matthew E. Falagas,[a,b,c] Evridiki K. Vouloumanou,[a] George Samonis,[d] Konstantinos Z. Vardakas[a,b]

Alfa Institute of Biomedical Sciences, Athens, Greece[a]; Department of Internal Medicine-Infectious Diseases, Iaso General Hospital, Iaso Group, Athens, Greece[b]; Department of Medicine, Tufts University School of Medicine, Boston, Massachusetts, USA[c]; Department of Internal Medicine, University of Crete School of Medicine, Heraklion, Greece[d]

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Address correspondence to Matthew E. Falagas, m.falagas@aibs.gr.

SUMMARY

The treatment of bacterial infections suffers from two major problems: spread of multidrug-resistant (MDR) or extensively drug-resistant (XDR) pathogens and lack of development of new antibiotics active against such MDR and XDR bacteria. As a result, physicians have turned to older antibiotics, such as polymyxins, tetracyclines, and aminoglycosides. Lately, due to development of resistance to these agents, fosfomycin has gained attention, as it has remained active against both Gram-positive and Gram-negative MDR and XDR bacteria. New data of higher quality have become available, and several issues were clarified further. In this review, we summarize the available fosfomycin data regarding pharmacokinetic and pharmacodynamic properties, the *in vitro* activity against susceptible and antibiotic-resistant bacteria, mechanisms of resistance and development of resistance during treatment, synergy and antagonism with other antibiotics, clinical effectiveness, and adverse events. Issues that need to be studied further are also discussed.

INTRODUCTION

The alarmingly increasing antibiotic resistance rates reported among both Gram-positive and Gram-negative pathogens necessitate the implementation of alternative treatment strategies. In view of the rather limited availability of novel antimicrobial agents, the reevaluation of older antibiotic agents seems to be an appealing option. Fosfomycin, an old and rather decommissioned antibiotic, which was previously used mainly as oral (p.o.) treatment for uncomplicated urinary tract infections (UTIs), currently attracts clinicians' interest worldwide. Particularly, the reported activity against pathogens with advanced resistance suggests that this antibiotic may provide a useful option for the treatment of patients with these difficult-to-treat-infections.

Origin and Chemical Structure

Fosfomycin is an old antibiotic agent, discovered in 1969 (1). It is a phosphoenolpyruvate (PEP) analogue that is produced by *Streptomyces* spp., namely, *Streptomyces fradiae* (ATCC 21096), *S. viridochromogenes* (ATCC 21240), and *S. wedmorensis* (ATCC 21239) (1). It may also be produced synthetically (2).

Fosfomycin is a molecule with a low molecular weight (MW) (138) (3). The molecular structure of fosfomycin differs in regard to the available drug formulations. Specifically, fosfomycin is available in two oral formulations, fosfomycin trometh-amine (or fosfomycin trometamol) ($C_3H_7O_4P \cdot C_4H_{11}NO_3$) Fig. 1A) and fosfomycin calcium ($C_3H_5CaO_4P$) (Fig. 1B), and one intravenous (i.v.) formulation, fosfomycin disodium ($C_3H_5Na_2O_4P$) (Fig. 1C).

Commercial Formulations

As mentioned above, the commercially available formulations for oral fosfomycin treatment are fosfomycin trometamol and fosfomycin calcium. Fosfomycin trometamol, which is a phosphonic acid derivative of fosfomycin, is available as (1*R*,2*S*)-(1,2-epoxypropyl)phosphonic acid compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1) (4). Its commercially available oral formulation consist of a single-dose sachet that contains white granules (4). The MW is 259.2 (4). Fosfomycin calcium salt is the second commercially available formulation for oral fosfomycin treatment. It consists of a white tablet of 500 mg of fosfomycin (titer) (4). The commercially available intravenous fosfomycin formulation consists of 1 to 8 g powder of fosfomycin disodium with succinic acid as sole excipient (https://www.diagnosia.com/de/medikament/infectofos-3-g, http://www.drugs.com/uk/fomicyt-40-mg-ml-powder-for-solution-for-infusion-leaflet.html, http://www.ern.es/wp-content/uploads/2013/01/ENG-FOSFOCINA-INYECTABLE.pdf).

Even though inhaled fosfomycin treatment seems to have potential as an appealing treatment option (5), an aerosolized formulation of fosfomycin that will enable drug delivery directly to the lungs is not commercially available yet. Fosfomycin disodium

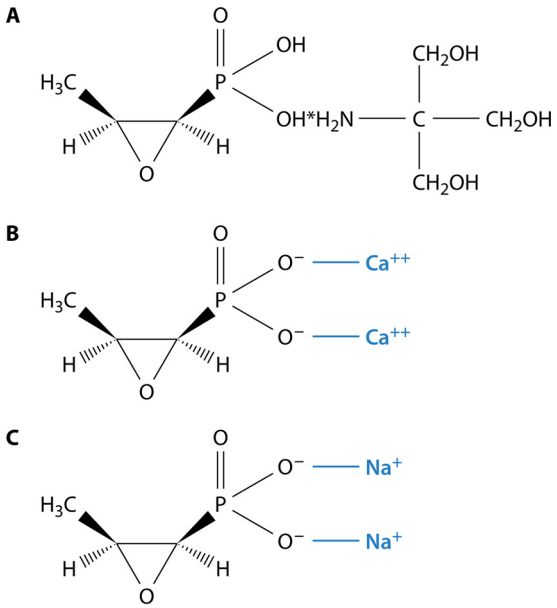

FIG 1 (A) Molecular structure of fosfomycin trometamol. (B) Molecular structure of fosfomycin calcium. (C) Molecular structure of fosfomycin disodium.

seems to be the preferred formulation for aerosolized fosfomycin, administered either as a solution for nebulization or as an inhaled dry powder via a metered dose inhaler or dry powder inhaler (6).

Use in Animals

Although fosfomycin has been studied in most of the domestic animals, it is not widely used in veterinary medicine except in countries in Central and South America (7). It is used primarily for the treatment of infectious diseases of broiler chickens and piglets. The drug is eliminated from animal tissues in 2 to 7 days, depending on the testing method, formulation or route of administration, and tissue or animal under study (7). In general, for both pigs and chickens, withdrawal times of 2 and 3 days after intramuscular and p.o. administration, respectively, could be assigned as a precautionary principle for public health (8).

ANTIMICROBIAL PROPERTIES

Mechanism of Action

Fosfomycin is a bactericidal antibiotic agent. It inhibits an enzyme-catalyzed reaction in the first step of the synthesis of the bacterial cell wall (9). Fosfomycin interferes with the first cytoplasmic step of bacterial cell wall biosynthesis, the formation of the peptidoglycan precursor UDP *N*-acetylmuramic acid (UDP-MurNAc) (10). Specifically, the enzyme UDP-*N*-acetylglucosamine enolpyruvyl transferase (MurA) is involved in peptidoglycan biosynthesis by catalyzing the transfer of the enolpyruvyl moiety of phosphoenolpyruvate (PEP) to the 3′-hydroxyl group of UDP-*N*-acetylglucosamine (UNAG) (11). Fosfomycin covalently binds to the thiol group of a cysteine (position 115 in *Escherichia coli* numbering; target Cys^{115}) in the active site of MurA and consequently inactivates it (11–13). This inhibitory action takes place at an earlier step than the action of β-lactams or glycopeptides.

For the entry inside the bacterium, fosfomycin uses two different uptake pathways (identified at least for *E. coli*), the L-alpha-glycerophosphate and the hexose-6-phosphate transporter systems (3). The activity of the second uptake system is induced by glucose-6-phosphate (G-6-P) (3). Moreover, the expression of the genes of both the above-mentioned uptake systems requires the presence of cyclic AMP (cAMP), along its receptor protein complex (3). Finally, fosfomycin reduces adherence of bacteria to urinary epithelial cells (14). In a similar manner, fosfomycin suppresses platelet activator factor receptors in respiratory epithelial cells, thus reducing adhesion of *Streptococcus pneumoniae* and *Haemophilus influenzae* (15).

Immunomodulating Activity

Fosfomycin exerts immunomodulatory effects by altering lymphocyte, monocyte and neutrophil function. It affects the acute inflammatory cytokine response *in vitro* and *in vivo*. It suppresses production of tumor necrosis factor alpha (TNF-α), interleukin-1β (IL-1β), and IL-1α and increases production of IL-10, while contradictory data have been published regarding IL-6 (15–18). On the other hand, concentrations of TNF-α, IL-1β, and IL-6 expressed as protein and mRNA were almost identical with and without fosfomycin in healthy volunteers (19). Fosfomycin suppresses IL-2 production from T cells (20), the production of leukotriene B4 (LTB4) from neutrophils, and the expression of IL-8 mRNA by LTB4 from monocytes (21). Fosfomycin also exhibits an immunomodulatory effect on B-cell activation (22). Fosfomycin enhances neutrophil phagocytic killing of invading pathogens (23), even in patients on chronic hemodialysis and renal transplantation (24). Fosfomycin resulted in enhanced bactericidal ability of neutrophils compared to other antimicrobials (25). The clinical relevance of the aforementioned actions remains to be elucidated.

Activity in Biofilms

Fosfomycin has the ability to penetrate into biofilms. Several experimental studies (*in vitro* and biofilm infection models) showed that fosfomycin, alone or in combination with other antibiotics, not only reduced or eradicated clinically significant bacteria from biofilms (26–30) but also resulted in modifications of the biofilm structure. In a rat cellulose-pouch methicillin-resistant *Staphylococcus aureus* (MRSA) biofilm model, combination therapy with vancomycin and fosfomycin resulted in the disappearance of biofilm-like structures (31). Reductions in the *Staphylococcus epidermidis* biofilm density were also observed with fosfomycin; the addition of azithromycin in one of the studies had no further effect on the biofilm density or bacterial eradication (32, 33). The combination of prulifloxacin and fosfomycin resulted in destruction and disappearance of *P. aeruginosa* multilayer biofilms from the surfaces of polyethylene tubes in a urinary tract infection rat model, as seen by scanning electron microscopy (34). Fosfomycin was able to reduce initial and mature *E. coli* biofilm forms on polystyrene tissue culture plates. Fosfomycin activity was enhanced when it was combined with *N*-acetylcysteine (35). Finally, fosfomycin was bacteriostatic against vancomycin-resistant enterococci (VRE) in urinary stents biofilms. The MIC_{90} of VRE strains increased from 64 mg/liter in planktonic cultures to 128 mg/liter in biofilm cultures (36).

Spectrum of Activity

In vitro susceptibility data suggest that fosfomycin is considerably active against both Gram-negative and Gram-positive pathogens. Specifically, fosfomycin is considered active against *Enterococcus* spp. (including *Enterococcus faecalis* and *E. faecium* irrespective of vancomycin resistance), *Staphylococcus aureus* (irrespective of methicillin resistance), and *S. epidermidis* (37, 38). Fosfomycin also exhibits considerable activity against Gram-negative pathogens, including *Salmonella* spp., *Shigella* spp., *E. coli*, *Klebsiella* and *Enterobacter* spp., *Serratia* spp., *Citrobacter* spp., and *Proteus mirabilis* (37–41). Fosfomycin has been also found to be active against *Listeria monocytogenes*, *Neisseria gonorrhoeae*, *Aerococcus urinae*, and *Helicobacter pylori* (42–45). Fosfomycin is not active against anaerobes, such as *Bacteroides* spp., but it is active against *Peptococcus* spp. and *Peptostreptococcus* spp. (46, 47). *Pseudomonas* spp., *Acinetobacter* spp., *Stenotrophomonas maltophilia*, *Burkholderia cepacia*, *Staphylococcus capitis*, *Staphylococcus saprophyticus*, and *Mycobacterium tuberculosis* are intrinsically resistant to fosfomycin (48, 49). *Morganella morganii* is also resistant to fosfomycin (50).

Intracellular Bactericidal Activity of Fosfomycin

Experiments have shown that some *S. aureus* strains, in part in the form of the small-colony variant, can resist intracellular killing after phagocytosis from neutrophils or persist inside the host cells, e.g., in the osteoblasts. In this way they can cause relapses of infections (51–53). Fosfomycin was shown to penetrate inside the cells

TABLE 1 Available fosfomycin MICs and zone diameter breakpoints according to the latest EUCAST and CLSI criteria[a]

Criteria[b]	Organism(s) and delivery route	MIC (mg/liter)			Zone diameter (mm)		
		S	I	R	S	I	R
EUCAST	*Enterobacteriaceae*						
	Intravenous	≤32		>32	NR		NR
	Oral[c]	≤32		>32	NR		NR
	Pseudomonas spp.						
	Intravenous[d]						
	Oral	NR		NR	NR		NR
	Staphylococcus spp.						
	Intravenous	≤32		>32	—[e]		—
	Oral	NR		NR	NR		NR
CLSI[f]	*E. coli*[g]	≤64	128	≥256	≥16	13–15	≤12
	E. faecalis[h]	≤64	128	≥256	≥16	13–15	≤12

[a] S, susceptible, I, intermediate, R, resistant; NR, not reported.
[b] EUCAST criteria are from version 5.0, 2015 (http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_5.0_Breakpoint_Table_01.pdf); CLSI criteria are from 2015 (48).
[c] For uncomplicated urinary tract infections.
[d] Epidemiological cutoff for wild-type isolates, ≤128 mg/liter.
[e] —, MICs are recommended.
[f] *Pseudomonas* spp., *Acinetobacter* spp., *B. cepacia* complex, *S. maltophilia*, *S. saprophyticus*, and *S. capitis* are considered to have intrinsic resistance, defined as inherent or innate (not acquired) antimicrobial resistance, which is reflected in wild-type antimicrobial patterns of all or almost all representatives of a species. Intrinsic resistance is so common that susceptibility testing is unnecessary.
[g] Testing and reporting only for *E. coli* urinary isolates.
[h] Testing and reporting only for *E. faecalis* urinary isolates.

and assist in bacterial clearance in cell line experiments. Compared to other antimicrobials, fosfomycin was more active than glycopeptides and daptomycin but less active than rifampin, ofloxacin, and clindamycin (51–53). Similarly, fosfomycin was able to reduce the intracellular concentration of *L. monocytogenes* (54). Both positive and negative data have been published regarding the ability of fosfomycin to eliminate intracellular *Salmonella enterica* serovar Typhimurium (54, 55), while fosfomycin's effectiveness in reducing intracellular *E. coli* was low (55).

IN VITRO DATA

Susceptibility Testing Methodology

The laboratory methods that have been used for the determination of *in vitro* susceptibility of Gram-positive and Gram-negative pathogens to fosfomycin include agar (Mueller-Hinton agar) dilution, broth dilution, disk diffusion, and Etest techniques (22, 40, 56–59). Supplementation of agar or broth with G-6-P enhances fosfomycin activity. In this regard, Mueller-Hinton agar or broth supplemented with 25 μg/ml G-6-P is recommended, as it results in maximal enhancement of fosfomycin activity (60). A recent study suggested that regarding *P. aeruginosa*, which lacks a specific G-6-P transporter, the addition of G-6-P in agar or broth does not affect fosfomycin activity (61). According to the Clinical and Laboratory Standards Institute (CLSI) standard criteria, the approved susceptibility testing methods are disk diffusion and agar dilution for urinary *E. coli* and *E. faecalis* isolates, whereas broth microdilution should not be performed (48). On the other hand, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) suggests both agar and broth (http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_5.0_Breakpoint_Table_01.pdf).

In an early study comparing agar dilution, broth microdilution, and disk diffusion for extended-spectrum β-lactamase (ESBL)-producing *E. coli* and *Klebsiella pneumoniae* isolates, excellent agreement was observed between the compared methods regarding *E. coli*, whereas considerable discrepancies were observed for *K. pneumoniae* (62). In a later study comparing disk diffusion with agar dilution for Gram-negative and Gram-positive isolates, *E. coli* was found to be uniformly susceptible (63). This finding was consistent regarding *K. pneumoniae* and *Enterobacter cloacae*, whereas the prevalence of resistance of *P. aeruginosa* and *S. maltophilia* was affected by the choice of MIC (63). On the other hand, particularly for *P. aeruginosa*, a recent study suggested that broth microdilution is a reliable method, whereas no concordance was observed between agar dilution and disk diffusion/Etest (61). Finally, a recent study evaluating agar dilution, disk diffusion, and Etest for contemporary multidrug-resistant (MDR) Gram-negative pathogens suggested that disk diffusion had poor performance for *Acinetobacter baumannii* and *Enterobacteriaceae* and that Etest performed poorly for all tested pathogens (64). The available MICs and zone diameter breakpoints suggested by CLSI and EUCAST for specific bacteria are presented in Table 1.

Susceptibility Reports (Gram-Negative and Gram-Positive Isolates)

Early *in vitro* reports suggested that fosfomycin exhibited considerable activity against Gram-negative and Gram-positive urinary isolates. In this regard, it was considered appropriate therapy for uncomplicated UTIs in many clinical settings worldwide. Specifically, fosfomycin exhibited considerable antimicrobial activity against Gram-negative urinary isolates, including *Enterobacteriaceae*, as well as Gram-positive urinary isolates, including *S. aureus* (both methicillin-susceptible *S. aureus* [MSSA] and MRSA) and *E. faecalis* (22). Yet, the reported activity of fosfomycin against *P. aeruginosa* and *Acinetobacter baumannii* was low (22). Specifically, according to the findings of a review published in 2009 that eval-

uated 22 studies, fosfomycin exhibited considerable activity against MRSA and penicillin-nonsusceptible pneumococcal isolates (cumulative susceptibility rates, 87.9% [4,240/4,892 isolates] and 87.2% [191/219 isolates], respectively) (65). Activity against vancomycin-resistant enterococci was less promising (cumulative susceptibility rate, 30.3% [183/604 isolates]) and more variable. In a concurrent review of 23 studies, fosfomycin was active against 30.2% (511/1,693 isolates) of MDR *P. aeruginosa* isolates (66). On the other hand, 3.5% (3/85 isolates) of MDR *A. baumannii* isolates and none of the 31 MDR *Burkholderia* species isolates were found to be susceptible to fosfomycin (66). Moreover, fosfomycin was found to be considerably active against MDR *Enterobacteriaceae* isolates (96.8% [1,604/1,657] of ESBL-producing *E. coli* isolates and 81.3% [608/748] of ESBL-producing *K. pneumoniae* isolates) (67).

In Vitro Activity against Contemporary Isolates (Studies Published after 2010)

In the current era, the emergence of MDR and extensively drug-resistant (XDR) pathogens complicated the therapeutic approach to serious infections, such as respiratory tract infections, bacteremia, and surgical infections. In addition, MDR pathogens are now frequently encountered in easy-to-treat infections, such as acute cystitis due to ESBL *E. coli* isolates. The above factors, as well as the limited options of novel antibiotic agents, necessitated the reevaluation of fosfomycin as a potential therapeutic option for infections caused by contemporary isolates with advanced antimicrobial resistance. Table 2 shows the susceptibility of contemporary bacteria to fosfomycin from the larger studies published from 2010 onwards (36, 56, 57, 61, 68–90).

Regarding Gram-positive bacteria, contemporary studies showed that fosfomycin is active against the majority of *S. aureus* strains (>90%), including MRSA, as well as coagulase-negative staphylococci (CoNS) (36, 56, 61, 72, 75, 82, 83, 87, 88, 90). However, one study reported that only 33.2% of MRSA strains were susceptible to fosfomycin (90). Similarly, fosfomycin activity against enterococci, including VRE strains, varied in the available studies, with some of the studies reporting activity as low as 30% (36, 91, 92). Resistance to fosfomycin did not seem to be associated with vancomycin resistance. In addition, fosfomycin seemed to be less active against *E. faecium* than against *E. faecalis* in some series (82, 91). Finally, in the study that provided comparative data, fosfomycin seemed to be less active against coagulase-negative staphylococci and streptococcal strains than against *S. aureus* (77.5% versus 61.9% versus 99.3%, respectively) (56).

The majority of the recently published studies evaluated the *in vitro* activity of fosfomycin against ESBL-producing *Enterobacteriaceae*, particularly *E. coli* and *K. pneumoniae* (68–71, 73, 74, 77–81, 84–86, 89). Although studies evaluating the susceptibility of isolates recovered from blood or respiratory specimens have been published, the great majority of these studies focused on urine samples. In general, fosfomycin was more active against *E. coli* (range, 82% to 100%) than against *K. pneumoniae* (15% to 100%). Community-acquired strains were in general more susceptible than nosocomial strains. Susceptibility of other *Enterobacteriaceae* was less frequently reported, but fosfomycin remained active against a significant proportion (72% to 97.5%); *P. mirabilis* was reported as the least susceptible of them. Finally, fosfomycin was found to be active against 90.5% to 100% of MDR *Enterobacteriaceae* (57, 76).

Fosfomycin was also evaluated against carbapenem-resistant (CR) or carbapenemase-producing Gram-negative bacteria (57, 76, 93). Most of the data refer to KPC-producing *K. pneumoniae* strains or, to a lesser extent, to other *Enterobacteriaceae*. MIC_{50} and MIC_{90} values were usually one dilution lower in ESBL-producing *K. pneumoniae* strains than in CR/KPC-producing *K. pneumoniae* strains. All CR *A. baumannii* strains were also resistant to fosfomycin (94), while 80.6% of CR *P. aeruginosa* strains were reported to be susceptible in one study (61).

The fosfomycin MIC distribution in the available studies was extremely variable and associated with several factors, including species, method used for determination of MIC, underlying fosfomycin resistance mechanisms and coexisting mechanisms conferring resistance to other antibiotics, and geographical region of isolation. Thus, MIC_{50} and MIC_{90} values were one dilution lower for ESBL-producing than for CR/KPC-producing *K. pneumoniae* strains (75, 88, 93). The presence of *rmtB* genes was also associated with higher MIC values in KPC-producing strains (95). Similarly, the susceptibility of ESBL-producing *E. coli* strains was slightly lower than that of strains with a nonspecific pattern of resistance. In general, *E. coli* (including ESBL-producing strains) and *S. aureus* (including MRSA) displayed a lower MIC distribution in studies published from 2010 onwards. In contrast, enterococci (particularly vancomycin-resistant *E. faecium*) and *K. pneumoniae* (especially CR strains) showed higher variation in MIC_{50} and MIC_{90} values. The susceptibility of *Proteus* spp. and *Enterobacter* spp. was similar to or slightly higher than that of *K. pneumoniae*, but the available data were limited. Compared with studies published before 2010, no major differences in the susceptibility of Gram-negative bacteria and *S. aureus* have been reported (65–67, 96). However, the cumulative susceptibility of VRE was found to be 30.3%, considerably lower than the susceptibility in studies after 2010 (65).

MECHANISMS OF RESISTANCE

Inherent Resistance

The mechanism of action and structure of fosfomycin are unique, making cross-resistance uncommon. However, several mechanisms conferring resistance to fosfomycin have been identified (96). Some bacteria are inherently resistant to fosfomycin. First, mutations in *murA* causing a change from cysteine to aspartate render bacteria (e.g., *Chlamydia* spp., *Mycobacterium tuberculosis*, and *Vibrio fischeri*) resistant to this antimicrobial agent (97) (49, 98). Second, a study reported the identification of a salvage pathway in peptidoglycan synthesis in *Pseudomonas putida*. Using this pathway, recycling of the peptidoglycan is accomplished instead of its *de novo* synthesis from UDP-MurNAc, which is the first peptidoglycan precursor (the production of which is catalyzed by MurA) (99). Consequently, the fosfomycin target (MurA) is not involved in peptidoglycan synthesis, resulting in inherent fosfomycin resistance. A similar pathway was recently described for *Pseudomonas aeruginosa* (10).

Acquired Resistance

In commonly fosfomycin-susceptible bacteria like *E. coli*, resistance develops when mutations occur in the uptake systems used as means of fosfomycin entry inside the bacteria (100). Mutations in the chromosomal *glpT* and *uhpT* genes, which encode fosfomycin transporters, result in blocked or decreased fosfomycin uptake

TABLE 2 Data on *in vitro* susceptibility of MDR or XDR bacteria to fosfomycin and relevant antibiotics from the larger studies published from 2010 onwards[a]

Category	First author, yr (reference)	Country, period	Method(s)	Source of infection	Resistance profile[b]	Organism(s)	No. of isolates	Susceptibility to fosfomycin (%)	Fosfomycin MIC_{50}, MIC_{90} (mg/liter)
Carbapenem-resistant or carbapenemase-producing Gram-negative bacteria	Jiang, 2015 (75)	China, 2010–2013	AD	NR	KPC	*K. pneumoniae*	278	39.2	64, >256
	Diaz-Aguilar, 2013 (61)	NR	AD, BMD	NR	CR (28.2)	*P. aeruginosa*	206	80.6	64, 256/512[d]
	Tuon, 2013 (88)	Brazil, 2010–2011	DD	Various	KPC-2	*K. pneumoniae*	311	99	NR
ESBL-producing *Enterobacteriaceae*	Cho, 2015 (73)	South Korea, 2008–2013	Microscan	UTI	ESBL	*E. coli*, *K. pneumoniae*	277	87.7 (*E. coli*, 94.9; *K. pneumoniae*, 61.7)	NR
	Sultan, 2015 (86)	India	DD	UTI	ESBL, AmpC	*Enterobacteriaceae* (*E. coli*, 90%)	372	98.9 (ESBL, 100; AmpC, 95.7)	NR
	Asencio, 2014 (69)	Spain, 2010–2012	Vitek II	Various	ESBL	*E. coli*	824	95 (ESBL, 82)	NR
						K. pneumoniae	136	88 (ESBL, 91)	
	Khan, 2014 (78)	Pakistan, NR	DD	UTI	ESBL	*Enterobacteriaceae*	381	Total, 84; *E. coli*, 93; *Klebsiella* spp., 64; *Proteus* spp., 50	NR
	Cagan Aktas, 2014 (71)	Turkey, 2011–2012	DD, Etest	UTI	ESBL (48.4)	*E. coli*	244	99 (ESBL, 97)	0.5, 3
	Sorlozano, 2014 (85)	Spain, 2006–2012	Wider, Microscan	UTI	ESBL (4.4–31.8)[c]	*K. pneumoniae*	3,271	40–78	NR
	Villar, 2014 (89)	Argentina, 2012–2013	DD	UTI	ESBL	*E. coli*	374	97.6 (ESBL, 98.2)	NR
	Villar, 2014 (89)	Argentina, 2012–2013	DD	UTI	ESBL	*K. pneumoniae*	94	94.7	NR
	Villar, 2014 (89)	Argentina, 2012–2013	DD	UTI	ESBL	*P. mirabilis*	50	72	NR
	Lai, 2014 (79)	China, 2004–2012	AD	UTI	ESBL (58.1)	*E. coli*	908	98.4 (ESBL, 93.8)	NR
	Karlowsky, 2014 (77)	Canada, 2007–2013	AD	Various non-UTI	ESBL	*E. coli*	254	94.9	2, 4
					AmpC		119	96.6	2, 16
	Morfin-Otero, 2013 (81)	Mexico, 2010–2011	BMD	NR	ESBL (16)	*E. coli*	75	96.9	≤32, ≤32
						K. pneumoniae	21		≤32, ≤32
	Sahni, 2012 (84)	India, 2009–2010	DD	UTI	ESBL (47.6)	*E. coli*	2,416	83 (ESBL, 81)	NR
	Araj, 2012 (68)	Lebanon	DD	UTI	ESBL	*E. coli*	374	86	NR
						K. pneumoniae	168	62	
	Briongos-Figuero, 2012 (70)	Spain, 2009	Vitek II, Etest	UTI	ESBL	*E. coli*	372	88.7	NR
						Klebsiella spp.	28	46	

	Lee, 2012 (80)	South Korea	AD	NR	ESBL	*E. coli*	165	92.9	NR
						K. pneumoniae	182	95.2	
	Hsu, 2010 (74)	Taiwan, 2008–2010	AD	Various	CR[c] (43–75), ESBL (42.7)	*E. coli*	72	99 (ESBL, 96)	1 and 32
						K. pneumoniae	167	87 (ESBL, 93)	16, 64
						E. cloacae	115	97	NR
						S. marcescens	25	84	NR
						C. freundii	20	95	NR
MDR *Enterobacteriaceae*	Kahlmeter, 2012 (76)	Europe, 2007–2008	DD	UTI	MDR (18.2)	*E. coli*	903	98.8	
	Falagas, 2010 (57)	Greece, 2007–2009	Etest	Various	MDR	*E. coli*	26	100	32, 64
						K. pneumoniae	116	90.5	1, 4
MDR Gram-positive bacteria	Champion, 2013 (72)	USA, 2008–2010	Etest, Vitek II	Cystic fibrosis	MRSA	*S. aureus*	277	99.6	
	Pogue, 2013 (82)	USA, 2008–201	Microscan, Etest	Various	VRE	*E. faecalis*	28	96	48, 96
						E. faecium	42	76	
	Descourouez, 2013 (36)	USA, 2007–2010	BMD	UTI	VRE	*E. faecium*	32	100	64, 64
	Rebiahi, 2011 (83)	Algeria, 2007–2009	DD	Surgical wound infections	MRSA	*S. aureus*	220	94.1 (MRSA, 93.3)	NR
	Taj, 2010 (87)	Pakistan, 2009	DD	Various	MRSA (31.6)	*S. aureus*	550	MSSA, 94.1; MRSA, 68.9	NR
	Yu, 2010 (90)	China, NR	DD	Various	MRSA	*S. aureus*	196	33.2	64, 128
	Falagas, 2010 (56)	Greece, 2008	DD	Various	Various	Gram positive	1846	*S. aureus*, 99.3; MRSA, 99.2; CoNS, 77.5	NR
	Endimiani, 2010 (93)	USA, 2009	Etest, AD, DD	NR	KPC	*K. pneumoniae*	68	62	16, 64

[a] Abbreviations: AD agar dilution; AMK amikacin; BMD broth microdilution; CR carbapenem resistant; DD disk diffusion; GNM, gentamicin; KPC, *Klebsiella pneumoniae* carbapenemase; MDR, multidrug resistant; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; NR, not reported; UTI, urinary tract infections; VRE, vancomycin-resistant *Enterococcus*; XDR, extensively drug resistant.
[b] The number in parentheses is the percentage of pathogens with the specific resistance pattern. If no percentage is provided, all isolates presented the resistance pattern.
[c] Refers to ertapenem-resistant bacteria.
[d] 256 with agar dilution and 512 with broth microdilution.

(92, 101). The encoded proteins are glycerol or carbohydrate transporters that are essential for metabolic functions or virulence in *E. coli* and other bacteria (96). Such mutations were the most common mechanisms of resistance in older series (102). Mutations in *cyaA* and *ptsI* genes (which result in lower cAMP levels and downregulation of fosfomycin transporters) have also been described and associated with a decrease in pilus biosynthesis and in the ability to adhere to epithelial cells (96, 103). Mutations in *murA* result in lower affinity of enolpyruvyl transferase for fosfomycin (104), while overexpression of the enolpyruvyl transferase was also shown to result in fosfomycin resistance (101).

Several fosfomycin-modifying enzymes have been described. FosA (glutathione *S*-transferase), the first to be described (in 1988), is a metalloenzyme transferred through plasmids in *Enterobacteriaceae*. It catalyzes the reaction between glutathione and fosfomycin to an inactive adduct (102, 105–107). New subtypes, with similar structure, of the gene have been described (*fosA2*, *fosA3*, *fosA4*, and *fosA5*) (108–110). Cooccurrence in plasmids with $bla_{\text{CTX-M}}$, bla_{NDM}, bla_{KPC}, bla_{OXA}, bla_{CMY}, bla_{AmpC}, bla_{TEM}, bla_{SHV}, $bla_{\text{SFO-1}}$, *gyrA*, *parC*, *parE*, *sul1*, *sul2*, *strA*, *strB*, *aac(6′)-Ib*, *aadA5*, *aphA6*, *tetA*(A), *mphA*, *floR*, *dfrA7*, *rmtB*, and *merA* genes has been reported, conferring resistance to β-lactams, quinolones, aminoglycosides, macrolides, sulfonamides, and tetracyclines (75, 80, 111–114). The genes conferring resistance to fosfomycin could be transferred together with genes conferring resistance to other antibiotics in either the same or a conjugate plasmid (114).

FosB is a similar enzyme (its amino acid sequence is 48% identical to that of FosA) that catalyzes the reaction between cysteine and fosfomycin in Gram-positive bacteria (plasmid encoded in *Staphylococcus* spp. and *Enterococcus* spp. and chromosomally in *Bacillus subtilis*) (102, 115–119). FosX is a chromosomal enzyme of *Listeria monocytogenes* that catalyzes the reaction of fosfomycin with water (120). FosC, found in *Pseudomonas syringae*, is an enzyme similar to glutathione *S*-transferase that catalyzes phosphorylation with ATP and inactivation of fosfomycin (121). Finally, kinases that cause fosfomycin degradation through phosphorylation (FomA and FomB, which are structurally and functionally related to FosC) have been identified in *Streptomyces* spp. and rarely in *P. aeruginosa* (122).

Heteroresistance

Heteroresistance to fosfomycin has been described for *S. pneumoniae*. In a recent study, 10 out of 11 tested strains showed heteroresistance to fosfomycin. All heteroresistant strains contained the MurA1 protein. When this was deleted, heteroresistance was abolished. The strain that did not show heteroresistance differed from the other strains by a single amino acid substitution in MurA1 [Ala(364)Thr]. When this gene was introduced into a heteroresistant strain, its heteroresistance phenotype was not changed. Thus, MurA is required for heteroresistance, but it is not the only factor involved (123). Heteroresistance was also described in MDR and non-MDR *P. aeruginosa* strains (124).

In Vitro and *In Vivo* Development of Resistance and Spread

Fosfomycin has been associated with rapid development of resistance *in vitro*, but widespread or increasing resistance in clinical practice has been infrequently reported (96). Several mechanisms can be associated with these observations. Nilsson et al. studied the development of resistance to fosfomycin in *E. coli* isolates *in vitro* and the behavior of fosfomycin-resistant isolates recovered from clinical specimens *in vitro* and in urine. They reported that development of resistance *in vitro* was highly probable and caused by mutations in *ptsI*, *cyaA*, *glpT*, *uhpA/T*, and other unspecified genes, while mutations in *ptsI* and *cyaA* were not observed in clinical isolates (103). All mutations developing *in vitro* caused a decrease in the bacterial growth rate of resistant pathogens (in laboratory media or in urine and in the presence or absence of fosfomycin) compared to that of susceptible isolates. Similarly, the growth rate was lower in resistant clinical isolates in the presence of fosfomycin (103).

As described above, in cases of lower urinary tract infections, such mutations may enable bacterial washout and provide a mean for preventing the isolates from establishing in the bladder. Furthermore, it has been postulated that the biological cost of these mutations could be high enough to prohibit the growth of the mutants in the intestines or outside the host (125). However, slower growth was not observed in fosfomycin-resistant clinical isolates in the absence of fosfomycin (103), suggesting that in real-case scenarios other compensatory mutations might ameliorate the biologic cost and enable persistence of resistant bacteria. The ability of fosfomycin to decrease adhesion of *E. coli* in the bladder wall and the high concentrations achieved in urine may further prevent bacterial establishment, at least in the urinary tract, even for isolates with a high fosfomycin MIC. Finally, the mutations described above can be found in chromosomes, but the emergence of resistant loci in plasmids (FosA and FosB) could potentially provide a better means for the spread of resistance mechanisms than the chromosomal ones (126). Several recently published studies have shown dissemination of fosfomycin-resistant strains (mainly due to the presence of FosA) in patients as well environmental reservoirs in livestock and animals (75, 113, 127, 128).

Fosfomycin administration was not as widespread as that for other antibiotics, e.g., β-lactams or fluoroquinolones. Thus, studies that did not account for fosfomycin consumption did not show major differences in fosfomycin resistance with time (96). However, in a study that evaluated 17,602 urinary tract infections due to *E. coli* during a 5-year period (2003 to 2008), a 50% increase in fosfomycin use resulted in an increase of fosfomycin-resistant, extended-spectrum β-lactamase (ESBL)-producing *E. coli* strains from 2.2% at the beginning of the study to 21.7% at the end ($P < 0.0001$) (129). A similar increase in fosfomycin resistance was reported among all isolates (from 1.6% in 2003 to 3.8% in 2008; $P < 0.0001$). A significant increase in fosfomycin resistance against uropathogens was reported in a second Spanish study during a 7-year period (2006 to 2012) (85). On the other hand, the limited available data from 5 randomized controlled trials (RCTs) included in a meta-analysis showed that resistance did not develop after a single-dose treatment for cystitis (130). These RCTs were conducted in Europe and the United States and included a total of 739 patients (nonpregnant women; children, 3%) (131–135). One disadvantage of this analysis was that 4 of these RCTs were published more than 15 years ago (1987 to 1998).

Older studies reported development of resistance during treatment in between 0% and 6.7% of all cases; development of resistance was more pronounced among *P. aeruginosa* strains (7 to 20%) (96). Recent *in vitro* experiments in 59 MDR and non-MDR *P. aeruginosa* strains confirmed the propensity of *P. aeruginosa* to develop resistance to fosfomycin (124). Although 61% of the studied strains were considered fosfomycin susceptible at the beginning of the study (MIC ≤ 64 mg/liter), they were replaced by

fosfomycin-resistant colonies even when the inoculum was low. We should acknowledge that heteroresistance was detected at baseline in all tested isolates (124). Development of resistance to fosfomycin during treatment along with an increase in β-lactam MICs was reported in 3 isolates in a Greek hospital. The resistant bacteria were considered mutants of the pretreatment ones (136).

SYNERGY AND ANTAGONISM

Table 3 shows the synergy of fosfomycin in combination with other antibiotics against clinically relevant bacteria.

Older Studies

Fosfomycin's unique mechanism of action provides a mean for possible synergy with other antibiotics. Older studies evaluating synergy of fosfomycin with other antibiotics against Gram-positive and Gram-negative bacteria were summarized in a review published in 2009 (137). The fractional inhibitory concentration index (FICI) and the efficacy time index (ETI) were used to define synergy. Time-kill experiments, checkerboards, broth microdilution, and agar dilution were used. Fosfomycin was synergistic with cefamandole, cefazolin, and methicillin for MRSA strains (138–140); however, data were discouraging for antibiotics more likely to be used for MRSA treatment, i.e., aminoglycosides, fusidic acid, and trimethoprim (140). Conflicting data were reported for vancomycin (139–141) and rifampin (139, 142). Other studies also showed synergy with ciprofloxacin and linezolid for MSSA strains (143, 144). Synergy against some strains of *Streptococcus* spp. was observed between fosfomycin and penicillin, cefminox, and cefotaxime but not vancomycin, imipenem, ceftriaxone, and cefepime (137). Regarding *Enterococcus* spp., synergy was observed with cefotaxime and for some strains with daptomycin and imipenem (137).

Fewer data were available for Gram-negative bacteria. Regarding *P. aeruginosa*, synergy was observed for most of the strains with aztreonam, cefepime, and levofloxacin, while conflicting or partially encouraging data were reported for imipenem, ceftazidime, ciprofloxacin, and aminoglycosides (137). One study showed synergy with ceftazidime, imipenem, and ciprofloxacin against only 1 of the 34 MDR *A. baumannii* strains and for 38% of strains with amikacin (145). Synergy was also observed between fosfomycin and gentamicin in some *E. coli*, *K. pneumoniae*, and *S. marcescens* strains (145).

Newer Studies

During the last few years, more data have become available regarding the potential synergistic activity between fosfomycin and other antibiotics against contemporary strains, for which fewer treatment options are available. The fractional inhibitory concentration index (FICI), reduction in colonies, and the efficacy time index (ETI) were used to define synergy. Time-kill experiments, checkerboards, broth microdilution, agar dilution, and Etest were used.

Nonfermenting Gram-negative bacteria. Two studies evaluated the potential synergistic activity between fosfomycin and colistin against OXA-23-producing *A. baumannii*; they reported synergy against 50% of the strains in one study (checkerboards were used) and 12.5% of strains in the other (checkerboards and time-kill assays were used) (146, 147). One of these studies reported synergy against 75% of strains when fosfomycin was combined with sulbactam (146). Discouraging results were reported when fosfomycin was combined with polymyxin B or minocycline for pan-drug-resistant *A. baumannii* strains (synergy was observed in 16% and 12% of strains using checkerboards and FICI, respectively) (148).

More promising data have been reported for CR *P. aeruginosa* strains; three studies reported synergy between fosfomycin and colistin (22%) or carbapenems (up to 40%) against clinical isolates using checkerboards and time-kill assays (40, 149, 150). Using checkerboards/FICI, aminoglycosides, piperacillin-tazobactam, ceftazidime, cefepime, and ciprofloxacin were also synergistic with fosfomycin against CR *P. aeruginosa* strains (151). In one more study, in which the resistance profile of *P. aeruginosa* was not reported, synergy (using FICI) between fosfomycin and aminoglycosides was observed for 60% to 80% of tested strains, with amikacin and isepamicin demonstrating the higher synergy rates (27). Against MDR *P. aeruginosa*, synergy against 50% to 70% of isolates (the Etest was used) was reported with carbapenems (mainly doripenem), while synergy with colistin, tigecycline, or netilmicin was reported for <15% of strains (59). However, we should note that other published studies reported no synergy against *P. aeruginosa* between fosfomycin and aminoglycosides or carbapenems using checkerboards and time-kill assays (6, 152).

Enterobacteriaceae. The available studies showed that synergy between fosfomycin and other antibiotics against *K. pneumoniae* depends on the underlying enzymes conferring resistance. The fosfomycin-doripenem, fosfomycin-aztreonam, and fosfomycin-aztreonam-amdinocillin combinations were highly effective in reducing bacterial populations of drug-resistant *K. pneumoniae* using checkerboards and time-kill assays (152, 153). In ESBL-producing *K. pneumoniae* strains, synergy with carbapenems (43% to 78%, with imipenem showing the highest rate), colistin (7%), netilmicin (43%), and tigecycline (21%) was reported (59). Against CR *K. pneumoniae* without specification of the exact mechanism of resistance, synergy with carbapenems (70%), colistin (36%), tigecycline (30%), and netilmicin (42%) was reported (59). The Etest was used in that study. Against KPC-2-producing *K. pneumoniae* strains, synergy with meropenem primarily (65%) and colistin secondarily (12%) was reported using time-kill assays, while combination with gentamicin resulted in indifference (154). Similarly, the fosfomycin-colistin and fosfomycin-colistin-meropenem combinations showed synergy against 2 VIM- and 2 NDM-producing *K. pneumoniae* strains (155). However, antagonism between colistin and fosfomycin against OXA-48-producing *K. pneumoniae* isolates was reported (checkerboards were used) (156). Regarding *E. coli*, the data refer to ESBL-producing strains; synergy was reported with carbapenems (by checkerboards, time-kill assays, and Etest), aztreonam (by checkerboards and time-kill assays), colistin (by time-kill assay and Etest), netilmicin (by Etest), and tigecycline (by time-kill assays and Etest) (28, 59, 152, 153, 157). In addition, synergy was reported with cefoxitin (by time-kill assays) at concentrations equal to the MIC of the isolate but not at higher concentrations (157). Finally, synergy was reported with colistin, but not with tigecycline, against NDM-1-producing *Enterobacteriaceae* using checkerboards (158).

Studies on *Neisseria gonorrhoeae* showed no synergy between several antibiotics (cefixime, ceftriaxone, azithromycin, colistin, ertapenem, gentamicin, minocycline, oxifloxacin, rifampin, and spectinomycin) and fosfomycin when the agar dilution or Etest method was used (159, 160). However, synergy was observed with ceftriaxone in a time-kill study (44).

TABLE 3 Synergistic activity of fosfomycin in combination with other antibiotics against several clinically relevant bacteria

Organism(s)	Antibiotics with activity in combination with fosfomycin (reference[s])		
	Synergy	Indifference	Antagonism
MSSA	Linezolid (174), ciprofloxacin (24), ceftriaxone (137), ciprofloxacin (137), rifampin (137)	Vancomycin (137), ceftriaxone (137), gentamicin (137)	
MRSA	Cefamandole (138, 139, 268), cefazolin (138, 139, 268), vancomycin (29, 137, 229), rifampin (29, 90, 142, 147), carbapenems (13, 152), cefmetazole (13), cefoperazone-sulbactam (13), linezolid (161), quinupistin-dalfopristin (162), fusidic acid (90), minocycline (163), tigecycline (29), daptomycin (29, 165)	Aminoglycosides (268), fusidic acid (268), trimethoprim (268), vancomycin (137)	Rifampin (139)
Glycopeptide-intermediate *S. aureus*	Imipenem (166), vancomycin (166), linezolid (166)		
CoNS	Ciprofloxacin (137), imipenem (137), rifampin (137)	Vancomycin (137)	
MR *S. epidermidis*		Vancomycin (167)	
Enterococcus	Cefotaxime (137), daptomycin (137),[a] imipenem (137)[a]		
VRE	Daptomycin (36), teicoplanin (92), amoxicillin (36), linezolid (36, 92),[b] ampicillin (92),[b] vancomycin (92),[a] tigecycline (92),[a] rifampin (92)[a]	Nitrofurantoin (92), minocycline (92)	Ampicillin (92)
Streptococcus spp.	Penicillin (137),[a] cefminox (137),[a] cefotaxime (137)[a]	Vancomycin (137), imipenem (137), ceftriaxone (137), cefepime (137)	
E. coli	Gentamicin (137)[a]		
ESBL-producing *E. coli*	Carbapenems (84),[a] aztreonam (153),colistin (84),[b] aminoglycosides (28, 84),[a] tigecycline (28, 84),[a] colistin (28)		
ESBL-producing *K. pneumoniae*	Carbapenems (84), colistin (84),[b] netilmicin (84),[a] tigecycline (84)[a]		
K. pneumoniae	Gentamicin (137)[a]		
MDR *K. pneumoniae*	Carbapenem (152), aztreonam (153)		
CR *K. pneumoniae*	Carbapenems (84, 164, 179), colistin (84, 164, 179),[a] tigecycline (84),[a] netilmicin (84)[a]	Gentamicin (179)	Colistin (156), (OXA-48-producing strain)
NDM-1-producing *Enterobacteriaceae*		Colistin (158), tigecycline (158)	
Salmonella	Amilacin (137),[a] cefepime (137)		
P. aeruginosa	Aztreonam (137),[a] levofloxacin (137),[a] ciprofloxacin (137),[a] cefepime (137),[a] gentamicin (137),[a] piperacillin (137),[a] ceftazidime (137),[a] imipenem (137)[a]	Imipenem (137), ceftazidime (137), ciprofloxacin (137), gentamicin (137)	
CR *P. aeruginosa*	Colistin (149),[a] carbapenems (149, 150),[a] aminoglycosides (27, 40), piperacillin-tazobactam (40), ceftazidime (40), cefepime (40), ciprofloxacin (40)		
MDR *P. aeruginosa*	Carbapenems (84), colistin (189),[b] tigecycline (84),[b] netilmicin (84)[b]	Carbapenems (152), aminoglycosides (168)	
Acinetobacter	Amikacin (137)[a]	Imipenem (137), ceftazidime (137), ciprofloxacin (137)	
OXA-23-producing *Acinetobacter*	Colistin (59, 89),[a,b] sulbactam (89)		
Pan-drug-resistant *Acinetobacter*	Polymyxin B (90),[b] minocycline (90)[b]		
N. gonorrhoeae	Ceftriaxone (44)	Cefixime (159, 253), ceftriaxone (159, 253), azithromycin (253), colistin (253), ertapenem (253), gentamicin (253), minocycline (253), oxifloxacin (253)	

[a] Synergy was observed in ≤50% of tested strains.
[b] Synergy was observed in <20% of tested strains.

Gram-positive bacteria. Several studies have evaluated the synergistic activity of fosfomycin with various antibiotics against *S. aureus*, especially MRSA. All these studies reported high synergy rates *in vitro* among clinical isolates (by time-kill assays and checkerboards): with doripenem (against 95% of isolates) (152), linezolid (98%) (161), quinupristin-dalfopristin (100%) (162), fusidic acid (88%) (90), and minocycline (87%) (163). Lower synergy was reported with rifampin (50%) (164). It is also noteworthy that antagonism was not reported for any of the above combinations. Similarly, *in vivo* biofilm models showed synergy between fosfomycin and vancomycin or daptomycin against MRSA strains (31, 165). Another study showed that the fosfomycin-rifampin combination was the most successful in reducing MRSA bacterial colonies (time-kill assay); other combinations tested in this study, in order of decreasing efficacy, were fosfomycin-daptomycin, fosfomycin-vancomycin, and fosfomycin-tigecycline (29). In a peritonitis model against a glycopeptide-intermediate *S. aureus* isolate, the combination of fosfomycin-imipenem was more effective than the combination of fosfomycin with vancomycin or linezolid (166). The effectiveness of these combinations was confirmed histologically (by disappearance of biofilm-like structures, marked decrease in necrosis, and formation of granular tissue) in the aforementioned studies. Finally, synergy between fosfomycin and vancomycin against methicillin-resistant *S. epidermidis in vitro* (by checkerboards) was not reported (167).

Two studies evaluated the potential synergistic activity between fosfomycin and other antibiotics against VRE clinical isolates. In general, synergy was observed *in vitro* with daptomycin, teicoplanin, and amoxicillin (by time-kill assays) (36, 91). Synergy was observed with linezolid or ampicillin against few vancomycin-resistant *E. faecalis* strains, while no synergy was reported with nitrofurantoin or minocycline (36, 91). Similar synergy between fosfomycin and vancomycin, tigecycline, or rifampin against both *E. faecium* and *E. faecalis* was reported (20% to 33%) (91). In biofilm models, synergy was observed against most *E. faecalis* strains with teicoplanin (44%), tigecycline (56%), or rifampin (100%), but these combinations were less successful against *E. faecium* (10%, 10%, and 40%, respectively). No synergy was observed in biofilm models with linezolid and ampicillin (91). In addition, antagonism between fosfomycin and ampicillin was reported for 2 VRE isolates.

Although some of these studies provide promising data for the selection of specific antibiotic combinations in real clinical scenarios in the future, it is evident that not all isolates would be susceptible to these combinations. For example, the same antibiotic combination (most notable and clinically relevant, fosfomycin with colistin, carbapenems, or aminoglycosides) resulted in variable synergy, or even antagonism, against CR *K. pneumoniae* isolates. It is probable that other coexisting mechanisms conferring resistance, including efflux pumps and modified antibiotic targets, and transferred together with ESBL genes in the same or conjugated plasmids contribute to these phenotypes. Enhanced antibiotic uptake (168) or downregulation of vital genes for bacterial growth (169), as shown for tobramycin in the presence of mucin and under anaerobic conditions in patients with cystic fibrosis, may also contribute to the synergistic activity. Future studies should compare the outcomes for patients infected by bacteria which were susceptible to antibiotic combinations *in vitro* to those for patients infected by bacteria that remained resistant.

PHARMACOKINETICS AND PHARMACODYNAMICS

Oral Fosfomycin

The oral bioavailability of fosfomycin trometamol ranges between 34 and 58% (38, 122). Absorption occurs in the small intestine, and evidence suggests that coadministration of fosfomycin trometamol with food may reduce absorption of the drug (37% fasting versus 30% with food) (4, 170). The maximum concentration in serum (C_{max}) was also higher under fasting conditions (12.1 ± 0.6 mg/liter and 7.8 ± 1.6 mg/liter, respectively), but urinary recovery rates were similar (58% versus 52%) (170). Age does not seem to affect absorption (38). Metoclopramide increases gastrointestinal motility and results in lower absorption and lower serum concentrations. The rate and extent of absorption of fosfomycin trometamol were approximately 6 times greater than those of fosfomycin calcium during the first 2 h postdose and approximately 3 to 4 times greater during the 12-h postdose period (4). In a study comparing the pharmacokinetic (PK) properties of fosfomycin trometamol and fosfomycin calcium, mean peak serum concentrations following a single 2-g dose of fosfomycin trometamol were found to be 2- to 4-fold higher than those obtained after a single 3-g dose of fosfomycin calcium (171). The reason for this observation is that fosfomycin calcium is hydrolyzed and thus inactivated by gastric acid (172–174).

The mean serum elimination half-life ($t_{1/2}$) of fosfomycin trometamol is estimated at 5.7 h (38). The $t_{1/2}$ was relatively prolonged in elderly patients (38). The area under the concentration-time curve (AUC) is 145 to 228 mg · h/liter (38) Conflicting data regarding the apparent volume of distribution has been published (40 to 136 liters) (94). The degree of binding of the fosfomycin molecule with proteins is negligible (174). Fosfomycin is excreted nonmetabolized in the urine, through glomerular filtration (175). Depending on age, fasting, and renal function, 11 to 60% of the drug can be found in the urine within 24 h from administration (122). Specifically, older age, administration with a meal, and deteriorating renal function result in slower elimination through the kidneys (122).

Following a single 3-g dose of fosfomycin trometamol, peak urine concentrations are reached within 4 h (38). High urine as well as bladder tissue concentrations (>128 mg/liter) are retained for 1 to 2 days, which is sufficient to eliminate the majority of common uropathogens (38, 176) However, the activity of fosfomycin at concentrations equal to the MIC is impaired against a variety of pathogens when the urine pH is below 6, resulting in bacterial regrowth (177). Contemporary published evidence suggests that following a single 3-g dose of oral fosfomycin trometamol, sufficient intraprostatic concentrations in uninflamed prostatic tissue are achieved (178).

No contraindications exist for the administration of fosfomycin with other medications. Unless the benefits outweigh the risks, typhoid (live attenuated) and BCG vaccines should be withheld in patients receiving fosfomycin, as with other antimicrobials, as the coadministration may lower vaccine effectiveness due to pharmacodynamic (PD) antagonism (http://reference.medscape.com/drug/formulary/monurol-fosfomycin-342560#3). Fosfomycin may increase the levels or effect of digoxin; patients should be monitored closely when digoxin and fosfomycin are coadministered. A low risk for contraceptive failure exists when fosfomycin is coadministered with conjugated estrogens. Minor or insignificant interactions may result in lower absorption of vitamin B

complex, metoclopramide, and balsalazide (http://reference.medscape.com/drug/formulary/monurol-fosfomycin-342560#3). Finally, fosfomycin trometamol should not be coadministered with probenecid, which decreases renal clearance and excretion of fosfomycin (4).

Parenteral Fosfomycin Disodium

In vivo studies suggest that following a 15-mg/kg intravenous dose of fosfomycin disodium in piglets, the AUC from 0 to 12 h (AUC_{0-12}) was 120.00 ± 23.12 μg · h/ml, whereas the volume of distribution was 273.00 ± 40.70 ml/kg; plasma clearance was 131.50 ± 30.07 ml/kg/h, and the $t_{1/2}$ was 1.54 ± 0.40 h (179). In the same study, following intramuscularly administered fosfomycin disodium, the AUC_{0-12} and bioavailability were 99.00 ± 0.70 μg · h/ml and 85.5% ± 9.90%, respectively (179). Another *in vivo* study evaluating a 20-mg/kg/day dose of intravenous/intramuscular fosfomycin disodium in cattle suggested that effective fosfomycin plasma concentrations for susceptible pathogens could be achieved up to 8 h after intravenous administration and approximately 10 h after intramuscular administration (180).

Following intravenous administration, variable peak, mean, and trough fosfomycin levels have been reported in humans. In general, peak concentrations were high (up to 606 mg/liter) (174). Nonrenal elimination of intravenous fosfomycin is negligible, with 93 to 99% excreted unchanged in the urine (22, 175, 181). With regard to fosfomycin's tissue penetration following intravenous administration in patients or healthy volunteers, a review suggested that intravenously administered fosfomycin has greater penetration into subcutaneous and muscle tissue, followed by lung and bone tissue (174). Substantial concentrations following intravenous doses were also achieved in cerebrospinal fluid (CSF), soft tissues, and bone tissues, whereas data regarding the distribution of fosfomycin into intra-abdominal sites were scarce.

Skin, soft tissue, and abscesses. Data from healthy volunteers and patients showed that fosfomycin achieves high concentrations in skin and soft tissues. In healthy volunteers, administration of a single 8-g dose of fosfomycin resulted in AUC_{0-8} ratios between the interstitial fluid of muscles and adipose tissue over that of serum of 0.53 and 0.71, respectively (182). In intensive care unit (ICU) patients with soft tissue infections, the AUC_{0-4} ratio for muscle over plasma was 0.71 (183). Similar findings were reported for diabetic foot infections with osteomyelitis (184). Fosfomycin also exhibited similar penetration into subcutaneous tissue regardless of the presence of inflammation (185). However, fosfomycin levels in the abscess fluid were highly variable. It seems that fosfomycin penetration into abscesses depends on morphological characteristics (e.g., the permeability of the outer wall or the vascularity of the surrounding tissues) beyond plasma concentrations or the individual ratios of abscess surface area to volume (186, 187).

An advantage of fosfomycin in the case of abscesses could be the increased bactericidal activity against both Gram-positive and Gram-negative bacteria (188). The MICs for fosfomycin were lower under anaerobic conditions. The culture media and the strains tested significantly affected the degree of change in MICs. The growth-inhibitory diameter in the paper disc assay increased in parallel with the decrease in the redox potential of the agar medium. As the increase of the activity of fosfomycin in anaerobic cultures was not associated with the change of medium pH or the change of mobility of the drug in agar, it was assumed that the uptake of fosfomycin through the cell membrane increases under anaerobic conditions (188).

Lower respiratory tract. An intravenously administered fosfomycin dose of 2 g was reported to achieve substantial concentrations of 12 to 16 mg/liter in healthy lung tissue, approximately half of that achieved in serum. The concentration in tumor cells was half of that in healthy tissue (189). In patients with tracheostomy, fosfomycin concentrations (7 ± 7.14 mg/liter) in bronchial secretions 2 h after the end of a 4-h infusion were 13% of those in serum (190). Intravenous fosfomycin seems also to exhibit good penetration into infected lung tissue; the ratio of the $AUC_{0-\infty}$ for lung to the $AUC_{0-\infty}$ for plasma was 0.63 in a study evaluating the ability of a single 4-g intravenous dose of fosfomycin to penetrate lung tissue of septic patients. In that study, fosfomycin's mean C_{max} and $AUC_{0-\infty}$ were higher in healthy than in infected lungs (131.6 ± 110.6 mg/liter versus 107.5 ± 60.2 mg/liter and 367.6 ± 111.9 mg · h/liter versus 315.1 ± 151.2 mg · h/liter, respectively) (191). Finally, fosfomycin achieves adequate concentrations in pleural fluid (due to both infectious and noninfectious etiology) for at least 12 h following the end of infusion. However, the presence of pachypleuritis may impede penetration in pleural effusion (192).

CNS and CSF. Fosfomycin crosses the blood-brain barrier, and meningeal inflammation increases its concentration in the CSF (193). However, an *in vitro* study showed that the antibacterial activity of fosfomycin against *S. aureus* was lower in CSF than in Mueller-Hinton broth, suggesting that fosfomycin may not be sufficient for isolates with higher MICs (194). In a rabbit model for pneumococcal meningitis, it was also suggested that fosfomycin concentrations in CSF should be at least 8 times higher than the MIC for the isolate in order to obtain adequate bacterial killing (195). Therefore, fosfomycin may not be considered adequate as monotherapy for patients with meningitis (195). In patients with CSF drainage, a single 5-g or 10-g dose resulted in CSF levels 9.2% and 13.8%, respectively, of those in plasma. When given at a dose of 5 g every 8 h, its CSF levels were 30 mg/liter or more after the second day of treatment and tripled in cases of inflammation (196). In a small study enrolling 6 ICU patients with ventriculostomy-associated ventriculitis, fosfomycin's AUC at steady state in CSF was 27% of that in plasma (197). Finally, data from 2 neurosurgical patients without central nervous system (CNS) infection showed that fosfomycin could achieve clinically relevant levels in the brain parenchyma (198).

Bone. Fosfomycin penetrates in both cortical and cancellous bone, and penetration correlates with plasma levels and the presence of inflammation. In patients undergoing hip replacement, a 4-h infusion of fosfomycin (4 g) resulted in a slightly higher concentration in cancellous than in cortical bone as measured 1 h and 3 h after the end of infusion (199). Much higher concentrations in the interstitial bone fluid were reported for patients receiving intravenous fosfomycin for chronic osteomyelitis or diabetic foot infections with osteomyelitis (184, 200).

Intra-abdominal sites. Although fosfomycin is eliminated almost entirely through the kidneys, its concentrations in the bile and gallbladder were high in patients undergoing cholecystectomy, especially soon after administration; its levels decreased gradually over time (201). In a study of 4 patients, fosfomycin achieved concentrations higher than the MIC for the causative bacteria in purulent ascitic fluid as well as in the inflamed appendix (202).

Heart valves and biofilms. In patients undergoing open heart surgery for valvulopathies, prophylactic administration of intravenous fosfomycin (5 g) resulted in variably high valve concentrations (27 to 77 mg/liter) depending on the degree of valvular degeneration. The levels were maintained for at least 60 min (203). Data regarding penetration of fosfomycin into biofilms have not been published, but several studies have evaluated the effectiveness of fosfomycin alone or in combination in experimental biofilm models (see below).

Concentration- or time-dependent action. It is not fully elucidated whether bacterial killing with fosfomycin is time or concentration dependent. It seems that this depends on the microorganism under study. Thus, it seems that for *P. aeruginosa* and *S. aureus*, fosfomycin demonstrates time- or non-concentration-dependent killing (6, 168). Recently, a study suggested that fosfomycin demonstrates both time- and concentration-dependent activity against *S. aureus* (13). On the other hand, concentration-dependent killing was demonstrated against *Enterococcus faecium*, *E. coli*, and *P. mirabilis* (36, 204).

Clinical Significance of PK and PD Aspects in Specific Patient Groups

Elderly individuals. Comparative pharmacokinetic evidence with regard to elderly and younger individuals suggested that the serum $AUC_{0-\infty}$ for both fosfomycin tromethamine and fosfomycin calcium was significantly increased in elderly compared to younger individuals (171). On the other hand, fosfomycin trometamol and fosfomycin calcium clearance was significantly decreased in elderly compared to younger individuals (171). Dose adjustment for both oral fosfomycin formulations is not recommended for elderly individuals with endogenous creatinine clearances of >50 ml/min per 1.73 m^2 (171). However, in elderly patients with impaired renal function (mean creatinine clearance of 40 ml/min), the fosfomycin urinary concentration was higher than that in healthy adults (205).

Children and neonates. In children 3 to 15 years old, the elimination half-life of fosfomycin is similar to or slightly lower than that in adults with normal renal function (206). However, the half-life is prolonged in both full- and preterm neonates due to their larger volume of distribution and lower glomerular filtration rate (207). High mean serum and urine concentrations are achieved; in addition, 58% to 78% of the dose is excreted in the urine (206). Early published evidence regarding the pharmacokinetic aspects of intravenous fosfomycin in children suggests a dose response in blood and urine concentrations of the drug, given at 25 mg/kg and 50 mg/kg either through intravenous injection or through a 1-h intravenous infusion (206). However, a recent study that focused on the pharmacokinetic and dosing aspects of fosfomycin treatment in children and neonates suggested that fosfomycin exhibits a time-dependent bactericidal activity (207).

Pregnancy and lactation. Fosfomycin trometamol has been assigned to pregnancy category B (i.e., animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women) (4); thus, it should be used during pregnancy only if clearly indicated (174). Fosfomycin is reported to cross the placental barrier through simple diffusion but does not affect the placental transport of other nutrients (208). Teratogenic effects have not been reported with fosfomycin doses of ≤1,000 mg/kg/day (corresponding to 1.4 and 9 times the human dose) in pregnant rats, whereas when doses of ≥1,000 mg/kg/day were administered to pregnant rabbits, fetotoxicities, concomitantly with maternal toxicity, were observed (4). Currently, there are no available data on excretion of fosfomycin in human milk. However, due to the low molecular weight of the drug, excretion is expected (4).

Critically ill patients. Pharmacokinetic data on intravenous administration of an 8-g dose of fosfomycin in critically ill patients with sepsis suggest that the drug exhibits a "tissue pharmacokinetic profile," with median fosfomycin concentrations in the interstitium and plasma exceeding MICs for *Streptococcus pyogenes*, *S. aureus*, and *Pseudomonas aeruginosa* for a period of 4 h (183). On the other hand, a more recent review suggested that the alterations in volume of distribution and creatinine clearance that are observed during critical illness may result in a need for fosfomycin loading doses and/or dose adjustments in order to avoid toxicity, as well as inadequate treatment (209).

Patients with renal function impairment. Since nonrenal clearance of fosfomycin disodium is negligible and fosfomycin trometamol is eliminated primarily in the urine, impairment of renal function was expected to affect the pharmacokinetic aspects of fosfomycin. Indeed, early data suggested that following a single dose of 3 g fosfomycin trometamol, the C_{max} and AUC were significantly higher in uremic patients with various degrees of renal insufficiency than in healthy controls (210). Early evidence also suggested that following injection of 1 g fosfomycin disodium, serum levels and time of elimination were related to the degree of renal insufficiency (211). Fosfomycin is also actively eliminated through the hemodialyzer (211–213). However, adjustment of the fosfomycin dose was not deemed necessary in critically ill patients under continuous venovenous hemofiltration (214). In addition, in a recent study focusing on the pharmacokinetic aspects of intravenous and intraperitoneal fosfomycin, in patients on automated peritoneal dialysis without peritonitis, fosfomycin exhibited good systemic exposure after intraperitoneal administration but limited peritoneal fluid penetration following intravenous administration (215).

DOSING GUIDELINES

Oral Fosfomycin

According to published bacteriological and clinical evidence, the recommended dose for oral fosfomycin trometamol treatment regarding uncomplicated urinary tract infections (cystitis) is a 3-g single dose (130, 216). Regarding complicated urinary tract infections (complicated cystitis), a higher-than-approved dose (a single oral dose of 3 g fosfomycin trometamol every 2 to 3 days for a total of 3 doses) (Table 4) is recommended by several authors (22). Evidence suggests that adjustment of the oral 3-g dose of fosfomycin trometamol is not necessary in vulnerable subpopulations, including pregnant women, elderly individuals, and patient with impaired renal/liver function (4, 22). However, regarding pediatric patients, lower oral dosages 1 to 2 g of fosfomycin trometamol have been reported in relevant studies (22, 132, 217, 218).

Parenteral Fosfomycin

The dose regimens for intravenous fosfomycin range with regard to the severity of the disease. Specifically, daily intravenous fosfomycin dosages in patients with normal renal function (creatinine clearance of ≥80 ml/min) range from a 12- to 16-g total daily dose, administered as 2 to 4 divided doses (22, 207, 219–221). In

TABLE 4 Studies with clinical outcomes after fosfomycin administration for urinary tract infections published from 2010 onwards[a]

First author, yr of publication (reference)	Study place, yr	Design	Patients, *n*	Infection	Bacteria	Fosfomycin treatment	Comparator	Mortality	Clinical cure	Microbiological cure
Ceran, 2010 (224)	Turkey, NA	RCT	Female adults, 260	Lower uUTI	*E. coli*, *Enterobacter* spp.	p.o. trometamol, 3-g single dose	Ciprofloxacin at 500 mg q12h for 5 days	NA	64/77 (83%) vs 53/65 (81%)	64/77 (83%) vs 51/65 (78%)
Usta, 2011 (226)	Turkey, 2007–2008	RCT	Pregnant females, 90	Lower uUTI	*E. coli*, *Enterobacter* spp., *K. pneumoniae*	p.o. trometamol, 3-g single dose	Amoxicillin-clavulanate at 625 mg q12h or cefuroxime at 500 mg q12h	NA	22/28 (79%) vs 46/56 (82%)	23/28 (82%) vs 48/56 (86%)
Palou, 2013 (225)	Spain, NR	SB RCT	Postmenopausal females, 118	Lower uUTI	*E. coli* (76.8%), *K. pneumoniae* (7.3%), *P. mirabilis* (4.9%), *Enterococus* spp. (3.7%)	p.o. trometamol, 3 g, 2 doses	Ciprofloxacin at 250mg q12h for 3 days	NA	32/37 (86.5%) vs 32/39 (82.1%)	23/37 (62.2%) vs 23/39 (59%)
Matsumoto, 2011 (227)	Japan, 2008	Prospective	Community infections, 40	Lower uUTI	*E. coli* (79.5%)	p.o. calcium, 1 g q8h for 2 days	NA	NR	34/40 (85%)	30/40 (75%)
Senol, 2010 (229)	Turkey, 2005–2006	Prospective	Community infections, 47	Lower cUTI	ESBL-producing *E. coli*	p.o. trometamol, 3 g every other day for 3 doses	Carbapenems	NA	21/27 (77.8%) vs 19/20 (95%)	16/27 (59.3%) vs 16/20 (80%)
Neuner, 2012 (230)	USA, 2006–2010	Retrospective	41	UTI	CR *K. pneumoniae* (13), *P. aeruginosa* (8), ESBL producers (7), VRE (7), *E. coli* (5)	p.o. in combination with other antibiotics in 27% of patients	NA	4/41 (10%)	NA	24/41 (59%); CR *K. pneumoniae*, 46%; *P. aeruginosa*, 38%; ESBL producers, 71%; VRE, 71%
Reid, 2013 (231)	USA, 2010–2011	Retrospective	Kidney transplantation, 14	UTI	ESBL-producing *E. coli* (7), KPC-producing *K. pneumoniae* (5), *P. aeruginosa* (2)	p.o. trometamol, 3 g, median of 3 doses	NA	NR	NA	4/13 (31%); recurrence, 7/13 (54%); persistence, 3/13 (21%)
Qiao, 2013 (228)	China, 2011	Prospective	Community infections, 356	Lower UTI	NR	p.o. trometamol, 3 g for 3 doses	NA	NR	uUTI, 179/189 (94.7%); recurrent UTI, 61/79 (77.2%); cUTI, 42/67 (62.7%)	uUTI, 83/85 (97.7%); recurrent UTI, 34/36 (94.4%); cUTI, 26/31 (83.9%)
Wu, 2014 (232)	Taiwan, 2003–2013	Prospective	Children with vesicoureteral reflux disease, 6	Recurrent UTI	*Enterobacteriaceae*, *P. aeruginosa*	100–200 mg/kg/day for 7–10 days plus amikacin at 15 mg/kg/day for 5 days or ceftazidime at 100–150 mg/kg/day for 7–10 days	NA	NR	1/6 (16.7%)	1/6 (16.7%)

[a] Abbreviations: CR carbapenem resistant; cUTI, complicated urinary tract infection; ESBL extended spectrum β-lactamase; KPC, *Klebsiella pneumoniae* carbapenemase; MDR multidrug resistant; NA, not available; NR, not reported; p.o., *per os*; q8h, every 8 h; RCT randomized controlled trial; SB, single blind; uUTI, uncomplicated urinary tract infections.

most cases, fosfomycin is administered intravenously as a dose of 8 g of fosfomycin disodium twice daily (every 12 h) (3). However, higher daily doses (up to 24 g) have been given to patients with CNS or other severe infections (220). Intravenous fosfomycin is administered as a slow infusion after dilution in 100 ml of normal saline.

With regard to patients with impaired renal function, currently it is not clear if dose adjustment is required for an estimated creatinine clearance of 40 to 80 ml/min. For patients with estimated creatinine clearances of 40, 30, 20, and 10 ml/min, a reduction to 70%, 60%, 40%, and 20% of the daily recommended dose, respectively, is proposed. In patients undergoing intermittent dialysis (every 48 h), 2 g after each session is recommended (https://www.medicines.org.uk/emc/medicine/28971). There are no data for dose reduction in patients with hepatic impairment or for elderly patients without renal impairment.

With regard to children and neonates, the dose of intravenous fosfomycin is adjusted according to body weight and age. Specifically, according to the instructions provided in the package insert of the intravenous fosfomycin formulation, the recommended doses are: 100 mg/kg in 2 divided doses for premature babies, 200 mg/kg in 3 divided doses in neonates, 200 to 300 mg/kg in 3 divided doses for infants up to 1 year (and up to 10 kg), and 200 to 400 mg/kg in 3 to 4 divided doses for children 1 to 12 years (http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con309596.pdf) (222). Published data regarding administration of fosfomycin through other parenteral routes (mainly intramuscularly) are scarce.

CLINICAL DATA

Urinary Tract Infections

The majority of the available clinical data regarding fosfomycin's effectiveness refer to treatment or prevention of lower UTIs, primarily cystitis. Current guidelines recommend fosfomycin for the treatment of female patients with uncomplicated cystitis. However, it was also stated that according to FDA data, 1 dose of fosfomycin may be associated with lower effectiveness than other short-course regimens (223). In contrast, pooled data from 27 RCTs on pregnant (16 trials) and nonpregnant (5 trials) females, males and nonpregnant females (3 trials), and children (3 trials) with cystitis or other lower UTIs did not support the FDA data (130). Most RCTs were open label and with a low mean Jadad score ($\leq$2). A single 3-g dose of fosfomycin was administered in these RCTs with cystitis patients. Comparator antibiotics included quinolones, β-lactams, aminoglycosides, nitrofurantoin, and sulfonamides. Clinical and microbiological cure, relapses, and reinfections were similar for fosfomycin and comparators. Pregnancy, gender, age, double blinding, and duration of administration of comparators did not affect clinical and microbiological success (130). Three additional RCTs evaluating the effectiveness and safety of fosfomycin for lower UTIs in females have been published since then (Table 4). All of them reported that fosfomycin trometamol was as affective as comparator antibiotics, regardless of the patients' hormonal or pregnancy status (224–226).

Besides RCTs, work on several cohorts studying the effectiveness of fosfomycin for the treatment of lower UTIs has been published (Table 4). These studies confirmed the effectiveness of fosfomycin for the treatment of patients with UTIs due to isolates susceptible to fosfomycin and several other antibiotics (227, 228) but also showed that fosfomycin monotherapy may not suffice for the treatment of recurrent UTIs or UTIs due to MDR bacteria in patients with significant comorbidity. In a small observational study of patients with complicated lower UTI due to ESBL-producing *E. coli*, oral fosfomycin trometamol was compared with carbapenem treatment. Clinical and microbiological success with fosfomycin and carbapenems was not significantly different (77.8% versus 95% and 59.3% versus 80%, respectively; $P > 0.05$) (229). In addition, a discordance between *in vitro* susceptibility to fosfomycin and microbiological effectiveness was observed in patients with *P. aeruginosa* (75% versus 38%) and CR *K. pneumoniae* UTIs (92% versus 46%) (230). Furthermore, in a small case series of kidney transplantation patients and children with vesicoureteral reflux disease, a high rate of recurrent infections was reported, mainly due to different or more susceptible bacteria than those for which fosfomycin was initially prescribed (231, 232). More robust data from well-designed and adequately powered studies should become available in order to reach safer conclusions. Finally, few case reports support fosfomycin use, alone or in combination with other antibiotics, for the treatment of patients with acute prostatitis (233–235).

Non-Urinary Tract Infections

The effectiveness of fosfomycin for the treatment of patients with Gram-negative or Gram-positive non-urinary tract infections has been evaluated in several studies since its discovery. In a comprehensive review of the older studies (until 2008), fosfomycin was effective in 84% of patients (81.1% cures; 1,302/1,604) (2). In the studies included in that review, fosfomycin was prescribed for various infections (pneumonia and other respiratory infections, osteomyelitis or septic arthritis, meningitis or encephalitis, ear, nose, and throat infections, obstetric and gynecological infections, septicemia or endocarditis, peritonitis, cervical lymphadenitis, eye infections, diabetic foot infections, and typhoid fever) due to several bacteria (most prevalently *S. aureus*, *S. epidermidis*, *P. aeruginosa*, *E. coli*, *K. pneumoniae*, and *Enterobacter* spp.) and in variable doses (1 to 24 g per day in 3 or 4 divided doses, when provided). Fosfomycin was administered primarily in combination with other antibiotics. In several cases it was administered when treatment failure with other antibiotics was documented. The duration of treatment was up to 2 months, depending on the infection under study (2).

An even older review that included studies performed in Japan soon after the discovery of fosfomycin reported that oral fosfomycin (*per os* 2 to 3 g/day for adults or 100 to 130 mg/kg for infants and children in most cases) was effective in 76% (912/1,200) of patients, while the parenteral form (i.v. 2 to 4 g/day for adults or 100 to 250 mg/kg for infants and children) was effective for 68% (340/500) (236). Fosfomycin in combination with other antibiotics was also found to be effective against MDR *P. aeruginosa* (90.9%; 30/33) and *S.* Typhimurium infections (66, 67). Finally, preliminary data suggest that fosfomycin is active against *H. pylori* and could be used as salvage therapy in patients not responding to first-line regimens (42, 237).

The major drawbacks of the aforementioned studies were the lack of randomization and the heterogeneity of patients under study, indications, and dosing of fosfomycin. In addition, several of them were conducted years or even decades ago, and their findings may not apply to the resistance profiles of contemporary isolates or the complexity and severity of diseases and infections that patients face nowadays. Data from RCTs are still not available, but

RCTs evaluating the comparative efficacy of fosfomycin and meropenem for bacteremic UTIs and fosfomycin in addition to daptomycin for MRSA bacteremia are under way (238, 239). Similarly, fosfomycin is being evaluated in combination with other antibiotics for MDR or XDR infections (NCT01297894, NCT02142751, and NCT00871104).

Table 5 summarizes the characteristics and outcomes of contemporary studies regarding the effectiveness of fosfomycin for the treatment of infections due to MDR bacteria (219, 220, 240–246). Fosfomycin was prescribed for several indications in variable doses and always in combination with other antibiotics. When provided, all-cause mortality ranged from 18.2% to 40.8%, values similar to those reported for combinations of colistin, tigecycline, and aminoglycosides (247–250). Importantly, 3 of the studies provided data regarding development of resistance during treatment; in 2 studies, resistant bacteria were not isolated, while 1 reported that 3 isolates developed resistance (220, 243, 246). Of note, the initial MIC of these isolates was at the highest within susceptible values (32 to 64 mg/liter; according to EUCAST, an MIC of 64 mg/liter denotes resistance). Infections due to such isolates have been associated with higher mortality (251, 252).

Prophylaxis

Increasing antimicrobial resistance, especially among quinolones, increased the interest in alternative prophylactic regimens for urologic procedures. In a recently published review regarding the effectiveness of fosfomycin in preventing UTI after endourological interventions or surgical procedures, the authors concluded that one or two doses of fosfomycin trometamol could be an effective alternative. The conclusion was limited by the small number of available patients for every indication (253). In an RCT not included in that review, fosfomycin (3 g by mouth every 48 h for two doses) was compared with ciprofloxacin (500 mg by mouth every 12 h for 5 days) for prevention of prostatitis after transrectal prostate biopsy; 671 patients were enrolled. Overall, complications were equally distributed between the compared antibiotics (22.6% versus 27.6%; $P = 0.17$). Bacteriuria was more frequently reported in patients receiving fosfomycin (8.6% versus 4.2%; $P = 0.02$), but resistance was more frequently reported after ciprofloxacin treatment (41.9% versus 69.2%; $P = 0.0004$). Both treatments were well tolerated (254).

In another, nonrandomized trial, fosfomycin prophylaxis after prostate biopsy was associated with fewer UTIs (5/104; 4.8%) than both levofloxacin (12/110; 10.9%) and ciprofloxacin (53/406; 13.1%), but microbiological failure was not significantly different (255). It seems that the administration of oral fosfomycin (3 g) 1 to 4 h prior to prostate biopsy results in concentrations in the prostate that are adequate to prevent infections due to bacteria with an MIC of <4 mg/liter (256).

Oral fosfomycin was also studied for the prevention of subsequent infections in 152 patients with recurrent UTIs. Fosfomycin at 3 g every week was compared to prulifloxacin at 600 mg every week, for a total of 12 doses. At the end of 3 months, recurrent UTI occurred in 50% of patients receiving fosfomycin and 63% of patients in the prulifloxacin arm; 9 months later, the corresponding figures were 68% and 73%, respectively (257).

Fosfomycin was evaluated in combination with metronidazole for prophylaxis in colorectal surgery in several RCTs published more than 2 decades ago, (125, 258) as well as for prophylaxis in upper gastrointestinal tract and hepatobiliary procedures (259). Although fosfomycin was as effective as comparators in these RCTs, it is not included in the recommended regimens in relevant guidelines (260–262). Finally, in an RCT, fosfomycin was compared with cefuroxime for knee arthroplasty. None of the fosfomycin-treated patients had an infection 6 months after surgery, compared to 1 patient presenting with superficial wound infection in the cefuroxime group (263).

Inhaled Preparations

The effectiveness of inhaled fosfomycin in combination with tobramycin for the treatment of patients with cystic fibrosis and chronic *P. aeruginosa* infection was evaluated in a double-blind, randomized, placebo-controlled trial. Patients were initially treated with inhaled aztreonam for 28 days (5). Two different dosage schemes (80/20 mg or 160/40 mg) were studied against placebo for another 28 days. Patients receiving both schemes of fosfomycin and tobramycin combinations showed significantly less decline in values for median forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) at the end of treatment and the time of randomization than patients who received the placebo (5). Changes in *P. aeruginosa* density in sputum between the end of treatment and the time of randomization were not significantly different between patients receiving the 160/40 mg fosfomycin-tobramycin combination and the placebo group (mean, 0.39 $\log_{10}$ CFU/g versus 0.67 $\log_{10}$ CFU/g; $P = 0.48$), but it was different between the group receiving the 80/20 mg fosfomycin-tobramycin combination and the placebo group (mean, -0.37 $\log_{10}$ CFU/g versus 0.67 $\log_{10}$ CFU/g; $P = 0.01$). The need for more antipseudomonal antibiotics, hospitalizations, and missed days at work or school during the study were not significantly different between the antibiotic combination groups at either dose and the placebo group (5). The efficacy of the amikacin-fosfomycin combination in mechanically ventilated patients for prophylaxis in colonized patients or treatment in patients with pneumonia is under evaluation in a clinical trial (NCT01969799).

ADVERSE EVENTS

Fosfomycin is contraindicated when known hypersensitivity exists, but it is generally considered safe (4). Mild and self-limited gastrointestinal disturbances, such as diarrhea (including from *Clostridium difficile*), nausea, abdominal pain, and dyspepsia, are the most common adverse events following oral administration. Headaches, dizziness, infections of the upper respiratory tract, vaginitis, and bacterial or fungal superinfections have been also reported. Transient laboratory alterations concern all blood series (neutropenia, eosinophilia, anemia, and low platelet count) and increases in liver enzymes and bilirubin but not renal function (22). In fact, studies in rats have shown that fosfomycin protects against aminoglycoside nephrotoxicity by inhibiting aminoglycoside-induced histamine release following mast cell destruction (265). Similar findings regarding vancomycin, amphotericin B, and cisplatin nephrotoxicity have been published (266–268). Clinical data confirming these observations are not available. In a meta-analysis of RCTs comparing oral fosfomycin with other antibiotics for the treatment of patients with lower UTIs, no significant difference was observed in the development of adverse events or withdrawals from the studies. However, fosfomycin was associated with fewer adverse events among pregnant women (130).

Sodium overload and hypokalemia are listed among the poten-

TABLE 5 Studies with clinical outcomes after fosfomycin administration for non-urinary tract infections published from 2010 onwards[a]

First author, yr of publication (reference)	Study place, yr	Design	Patients, *n*	Infections (*n*)	Bacteria	Fosfomycin	Comparator	Mortality	Clinical cure	Microbiological cure
Michalopoulos, 2010 (220)	Greece, 2008	Prospective	Adults, 11	ICU infections	CR *K. pneumoniae*	i.v. 4 g q6h plus other antibiotics	NA	2/11 (18.2%)	NR	NR
Apisarnthanarak, 2010 (219)	Thailand, 2009–2010	Retrospective	Adults, 8	HAP/VAP	CR *P. aeruginosa*	i.v. 2 g q8h plus i.v. doripenem (1 g q8h, extended infusion)	NA	2/8 (25%)	6/8 (75%)	6/7 (86%)
Florent, 2011 (243)	France, 2005–2010	Retrospective arm, prospective arm	Adults, 72	BJI (33), CNS infections (11), EaS infections (9), UTI (9), BSI (5), SSTI (4), pneumonia (1)	*Enterobacteriaceae* (24, including 5 ESBL- and 4 AmpC-producing strains), *P. aeruginosa* (13, including 5 MDR strains), staphylococci (12, including 6 MRSA strains); overall, MDR, 28%	i.v. 4 g q8h plus other antibiotics	NA	NR	63/72 (87%)	NR
Kusachi, 2011 (244)	Japan, NA	NA	Adults, 114	Intra-abdominal abscess	NA	i.v. added on previously failing antibiotic	NA	NR	91/104 (87.5%)	NA
Dihn, 2012 (242)	France, 2007	Prospective	Adults and children, 116	Lung infections (33), BJI (32), UTI (16), BSI (9), IAI, endocarditis, CNS infections (7)	*P. aeruginosa* (43), *Enterobacteriaceae* (29), MRCNS (23), MRSA (15), *Streptococcus* spp (6), MDR (83), ESBL (49)	i.v. 4 g q6h–q8h plus other antibiotics	NA	30/116 (25.9%)	77/99 (77%)	66/83 (79.5%)
Apisarnthanarak, 2012 (240)	Thailand, 2007–2011	Retrospective	49	HAP/VAP	CR *P. aeruginosa*	i.v. for ≥2 days plus doripenem (1 g q8h) or colistin (5 mg/kg/day in 2 divided doses)	NA	20/49 (40.8%)	29/49 (59.2%)	33/49 (67.3%)
Navarro-San Francisco, 2013 (245)	Spain, 2010–2012	Prospective	5	Bacteremia	OXA-48-producing *K. pneumoniae*	i.v. plus either tigecycline or colistin	Combinations of tigecycline, colistin, carbapenems, aminoglycosides	2/5 (40%) vs 24/35 (68.6%)	NR	NR
Pontikis, 2014 (246)	Greece 2010–2012	Prospective	ICU, 66	Primary BSI, VAP, CR-BSI, IAI	KPC-producing *K. pneumoniae* (41), *P. aeruginosa* (17)	i.v. 16–24 g in divided doses plus other antibiotics	NA	18/48 (37.5%)	26/48 (54.2%)	27/48 (56.3%)
Del Rio, 2014 (241)	Spain, 2001–2010	Prospective	16	BSI (75% endocarditis)	MRSA	i.v. 2 g q6h plus imipenem (1 g q6h)	NA	5/16 (31%)	NR	NR

[a] Abbreviations: BJI, bone and joint infections; BSI, bloodstream infections; CNS, central nervous system; CR, carbapenem resistant; CR-BSI, catheter-related bloodstream infections; EaS, ear and sinus infections; ESBL, extended-spectrum β-lactamase; HAP, hospital-acquired pneumonia; IAI, intra-abdominal infections, i.v., intravenous; KPC, *Klebsiella pneumoniae* carbapenemase; MDR, multidrug resistant; MRCNS, methicillin-resistant coagulase-negative staphylococci; MRSA, methicillin-resistant *S. aureus*; NA, not available; SSTI, skin and soft tissue infections; UTI, urinary tract infections; VAP, ventilator-associated pneumonia.

tial adverse events after i.v. administration. Every gram of i.v. fosfomycin contains 0.32 g of sodium (222). In addition, fosfomycin is thought to increase potassium urinary excretion in the distal part of the renal tubules. In a French study, hypokalemia was reported in 26% of patients (19/72) (243). The authors reported that while potassium was administered in all patients, hypokalemia was found only when fosfomycin was administered in 30- to 60-min infusions, while it did not occur when the period of administration was extended to 4 h. Other adverse events reported in that study were infusion site reactions (4%), heart failure and hypertension due to sodium overload (6%), and alanine aminotransferase increase (1%) (243). Thus, potassium supplements should be administered and its levels monitored regularly in patients receiving fosfomycin. Caution is also required in patients with heart failure.

Finally, fosfomycin was not mutagenic or genotoxic in the Ames test in cultured human cells (lymphocytes), in Chinese hamster cells, and the *in vivo* mouse micronucleus assay. Fosfomycin did not affect fertility or reproductive performance in male and female rats (4).

CONCLUDING REMARKS

Fosfomycin has been used since its discovery mainly for the treatment of outpatients with UTIs. It has a unique mechanism of action that makes cross-resistance uncommon and allows for synergy with other antibiotics. In addition, it has a broad spectrum of activity and is still active against several of the contemporary problematic antibiotic-resistant bacteria. It penetrates adequately, and its levels are maintained in human tissues. Thus, interest in its effectiveness against MDR or XDR nosocomial infections, when limited treatment options are available, has been reawakened. There is also interest in its potential synergistic activity with glycopeptides, rifampin, or daptomycin against MRSA infections as well as in monotherapy against infections with ESBL-producing *Enterobacteriaceae*. Although the current microbiological data favor its use, there are few clinical data regarding both effectiveness and safety. The currently available data derive from case series or small cohorts, in which fosfomycin was administered mainly in combination with other antibiotics. In addition, it may prove to be useful for the treatment of other infections, such as *H. pylori* infection, when first-line antibiotic regimens fail. Also, there is a lack of data comparing the trometamol and calcium salt oral preparations. Finally, its safety profile should be better studied in order to avoid serious adverse events such as hypokalemia and congestive heart failure.

There is insufficient evidence for widely accepted breakpoints for all bacteria besides *Enterobacteriaceae*, *Staphylococcus* spp., and *E. faecalis*. Thus, most studies extrapolate these breakpoints to other bacteria, such as *P. aeruginosa*, which is classified by the CLSI as inherently resistant to fosfomycin but for which several studies reported variable susceptibility rates. Accordingly, discordance between susceptibility to fosfomycin and effectiveness of fosfomycin monotherapy against UTIs due to *P. aeruginosa* was reported. In the same time, synergy and higher effectiveness was reported when combination treatment with other antibiotics was employed. In addition, there is a discrepancy between EUCAST and CLSI criteria for susceptibility, making interpretation and comparison of results from different studies difficult. Concerns over the potential development of resistance should prompt clinicians to use it judiciously in order to prevent the development of resistance inside hospitals and to prevent the dissemination of resistant strains from outpatients to inpatients.

In an era of antibiotic resistance and limited new treatment options, interest in fosfomycin is expected to culminate in the next decade. Several issues regarding effectiveness, safety, and resistance need to be addressed, namely, the susceptibility breakpoints, the appropriate dose and duration of administration for both oral and intravenous formulations, the effectiveness of oral fosfomycin for the treatment of complicated UTIs or non-UTIs, the everlasting question of the effectiveness of monotherapy and combination regimens (including existing [e.g., polymyxins, aminoglycosides, and glycopeptides] or forthcoming [e.g., combinations of β-lactams and new β-lactamase inhibitors, new aminoglycosides, or polypeptide antibiotics] antibiotics), and the concerns over increased probability of development of resistance during treatment. Finally, the intravenous formulation is not available in several countries, including the United States. In a recent case report, the oral formulation was used successfully for a bacteremic MDR infection (269).

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Matthew E. Falagas, M.D., M.Sc., D.Sc., is founder and director of the Alfa Institute of Biomedical Sciences (AIBS), Athens, Greece, Adjunct Associate Professor of Medicine at Tufts University School of Medicine, Boston, MA, and Director of the Department of Internal Medicine-Infectious Diseases, Iaso General Hospital, Iaso Group, Athens, Greece. His research interests include antimicrobial resistance and nosocomial infections. Prof. Falagas is the author of more than 650 peer-reviewed original papers, reviews, and editorials that received more than 30,000 citations. His current Hirsch index (h-index) is 87.

Evridiki Vouloumanou, born in 1984, studied medicine at the Medical School of the National and Kapodistrian University of Athens, Greece, during the period 2001 to 2007. She has been working as a research fellow in the Alfa Institute of Biomedical Sciences (AIBS) in Athens, Greece, since 2008, with a particular interest in pediatric infection diseases and antimicrobial agents. She currently holds a position as a pediatric resident in a tertiary care hospital in Athens, Greece.

George Samonis is a medical oncologist and infectious diseases specialist, Professor of Medicine, at the University of Crete, Greece. He studied at the University of Athens, Greece, and holds a doctoral degree from the same university. He has served at the M. D. Anderson Cancer Center in Houston, TX, USA, as a fellow and the University of Crete as Head of the Department of Hematology and Head of the Department of Internal Medicine of the University Hospital of Heraklion. His research resulted in 260 articles that have attracted ~8,100 citations; he is coinventor of two antifungal formulations. He has participated in 300 congresses and has given 60 lectures at scientific institutions. Dr. Samonis has been on the editorial boards of three medical journals and is reviewer for several others. He is member of 15 medical societies and has been the President of the Hellenic Society of Medical Mycology. His main interest is infections in immunocompromised hosts, with emphasis on fungal infections.

Konstantinos Z. Vardakas was born in Kozani, Greece. He obtained his medical degree from the National University of Athens School of Medicine in 2002. He obtained his Ph.D. in prophylaxis against fungal infections in special populations from the University of Crete School of Medicine. He completed his training in internal medicine in 2010. He is currently senior researcher in infectious diseases at the Alfa Institute of Biomedical Sciences and internist at Iaso General Hospital in Athens, Greece. He is interested in the treatment of patients with multidrug-resistant Gram-negative and Gram-positive infections and in prophylaxis against fungal and microbial infections in special populations.