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REVIEW

Fosfomycin and Its Application in the Treatment of Multidrug-Resistant *Enterobacteriaceae* Infections

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Abstract: The use of fosfomycin has been limited in therapeutics in recent years. Because it has shown good antibacterial activity in vitro and clinical efficacy in some domains, it has been proposed as an alternative to current antimicrobial agents, which are subject to increasing resistance. This paper reviews the main properties of fosfomycin and the latest publications concerning multidrug-resistant *Enterobacteriaceae* infections. In uncomplicated urinary tract infections, a single oral dose was found to be safe and effective. In complicated urinary tract infections, the same results were observed with several doses. In both cases, by using fosfomycin to treat infections, the use of carbapenems could be reduced, leading to lower costs and better microbial ecology. In severe infections, combinations with intravenous fosfomycin need to be explored further because its future activity may depend on choosing a good partner drug. Because of the fast evolution of microbial resistance, more studies are urgently needed.

Keywords: Fosfomycin, Antibacterial in vitro activity, Pharmacology, Clinical studies, Multidrug-resistant Enterobacteriaceae

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Introduction

Increased antibiotic resistance in *Enterobacteriaceae* is now a major concern worldwide.[1–7] Resistance is generally encoded by plasmidic or chromosomal genes which are easily transferred from one bacterium to another, without any consideration of species or genus limits. These transfers are generally of interest to microbiologists trying to discover the new β-lactamase able to hydrolyze all the β-lactam antibiotics, carbapenems included. This enzyme will be more devastating if its gene is incorporated into an integron capable of encoding resistance to all the antibiotics commonly used in therapeutics.[8–11] For practical purposes, a bacterial strain is said to be multidrug-resistant if it is resistant to at least three classes of potentially active antibiotics. It is said to be extensively drug-resistant if it is resistant to all but one or two antimicrobial agents.

Far from these descriptions, fosfomycin still exhibits good antibacterial activity,[12–17] mainly because its use has been limited in therapeutics. This underutilization was probably due to early problems in determining its true in vitro activity,[15] demonstrating its efficacy as a single agent,[15,18] and the resulting lack of inclination of pharmaceutical companies to perform clinical studies of fosfomycin in combination regimens. As a consequence of its spectrum of activity, low percentage of resistance, bactericidal effect, and pharmacokinetic properties, a single 3 g dose taken orally has been shown to be generally safe and effective in the treatment of lower urinary tract infections. Moreover, parenteral administration may be useful in the treatment of severe infections. Because multidrug-resistant *Enterobacteriaceae* are often responsible for these infections, not only in hospitals but also in the community, we have to bear these pathogens in mind, because secondary bacteremia may occur if treatment is not effective. We undertook this review to consider the place of fosfomycin in the treatment of these infections, because it has been recommended by many authors.[15,19–24]

Pharmacokinetics and Pharmacodynamics

Description

Fosfomycin is a small hydrophilic molecule (molecular weight 138 Da in its acidic form) that has two unusual features in its configuration, ie, an epoxy ring responsible for its antibiotic activity and a direct carbon-phosphorus link.[25] It is available principally as a disodium salt and as a trometamine (or trometamol) salt (Fig. 1). Initially released by a few bacterial species, such as *Streptomyces* spp[26–28] or *Pseudomonas syringae*,[29] it is now produced synthetically for pharmaceutical purposes. The disodium salt is administered parenterally and the trometamine salt orally.

Fosfomycin has a broad spectrum of activity against aerobic bacteria. It acts as an analog of phosphoenolpyruvate by inactivating the bacterial enzyme, enolpyruvatetransferase. Because this target is very specific to the bacterial wall, fosfomycin is not metabolized in mammals.[30,31]

In spite of its wide spectrum of antibacterial activity, pharmaceutical development of the molecule has been limited as a consequence of difficulties in determining its in vitro activity[15] and its clinical efficacy.[18,32] These issues have led to restricted therapeutic use of fosfomycin as a single agent. However, at the present time, when there is a shortage of antibiotic research and a dramatic development of antimicrobial resistance,[33–42] previous prescribing habits must be reconsidered and better use made of the old antimicrobial agents, like fosfomycin.

Pharmacokinetics of intravenous fosfomycin

After intravenous administration, the graphic representation of fosfomycin concentrations in the blood as a function of time shows an exponential trajectory (fast disposition phase) followed by a rectilinear phase (slow distribution phase).[25,30,31] This pattern is characteristic of a bicompartmental model. A cumulative effect is observed after multiple doses.[31,43] The main pharmacokinetic parameters are presented in Table 1. Serum protein binding is estimated at below 3%, which allows a large tissue availability.[29,44] The half life in serum is long, principally because of the slow renal clearance of fosfomycin. The apparent volume of distribution is large, suggesting good diffusion into interstitial fluid and access to infected tissues. The results of several studies showing fosfomycin distribution in the body after intravenous infusion are presented in Table 2. High bone and lung diffusion suggests that the drug would be effective in treating bone and lung infections. It should be noted

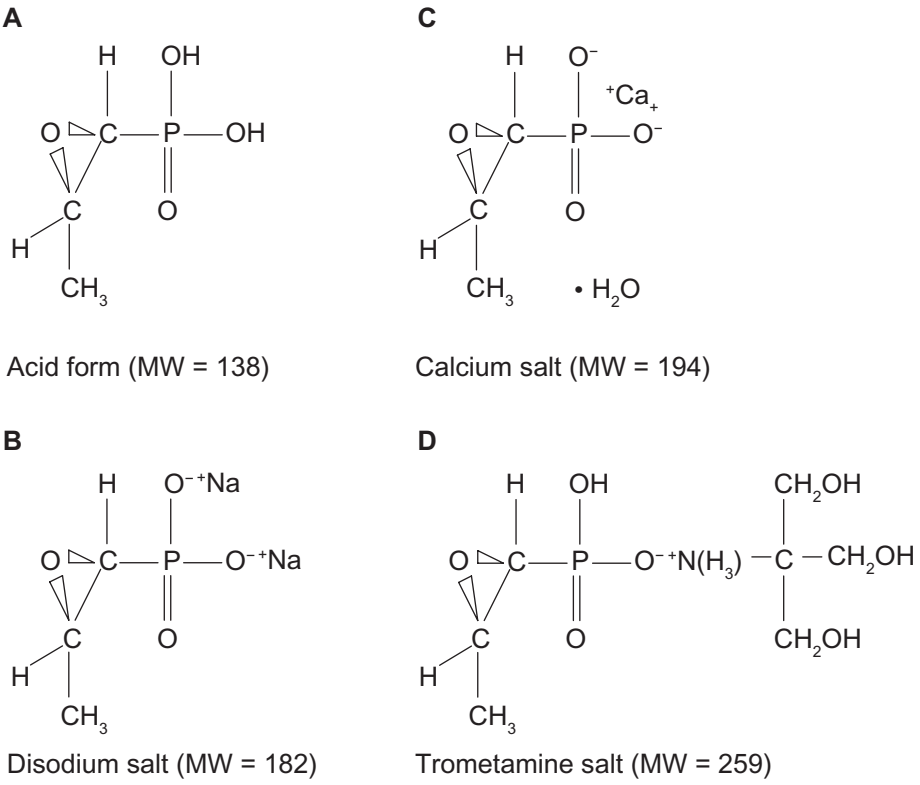

Figure 1. Structure and formulations of fosfomycin.

that fosfomycin concentrations in cerebrospinal fluid are much greater during the acute phase of meningitis than in the absence of inflammation.[31,45] Moreover, fosfomycin concentrations in amniotic fluid, fetal blood, colostrum, and milk were 45%, 18%, 5%, and 4%, respectively, of blood concentrations.[30]

Fosfomycin is almost completely eliminated by glomerular filtration, and 80%–95% of the dose is recovered unchanged in urine within 24 hours.[25,44] Bile concentrations of fosfomycin were observed to be 6% and 21% of blood concentrations in the studies by Kirby[30] and by Bando and Toyoshima, respectively.[46] Reduced renal function increases serum peaks and lengthens the plasma elimination half-life because fosfomycin is mostly eliminated by glomerular filtration.[47] When creatinine clearance is below 50 mL/min, the dose should be reduced by 50%.[48] The high prevalence of renal impairment in the elderly may require dose adjustment. Impairment of hepatic function has little impact on the plasma elimination half-life of fosfomycin.[44]

In spite of 40 years of evolution of methods to determine fosfomycin concentrations, there has been almost no progress in lowering the limit of sensitivity of the assays, which is approximately 1 mg/L by gas chromatography[43,49,50] or by capillary gas chromatography,[51,52] while by microbiological methods, it is reported to be 0.7–1.5 mg/L when mentioned.[47,48,53,54]

Pharmacokinetics of fosfomycin trometamine

The calcium salt of fosfomycin was quickly abandoned because of its low bioavailability, and the trometamine salt was preferred for its stability and better absorption.[44,48,53] Fosfomycin trometamine is thought to dissociate into fosfomycin acid and trometamine at the absorption stage,[55] and then fosfomycin absorption is mediated via the intestinal phosphate transport system.[56]

After a single dose of fosfomycin 3 g, the bioavailability ranges from 34% to 58%,[31,44,53,55,57] with a peak plasma concentration ranging from 12 to 32 mg/L and a delay of 2–4 hours. Because fosfomycin is not metabolized and the nonrenal clearance is negligible,[30] the main route of excretion is in the urine. Shortly after the peak in serum, the peak of excretion is observed, with urinary concentrations

Table 1. Pharmacokinetic parameters of intravenous fosfomycin.

Study subjects; age; gender	Fosfomycin dosage and administration	Serum concentration (mg/L)	Serum half-life $t_{1/2}\beta$ (hours)	V_D (L) or (L/kg)*	Systemic clearance (mL/min) or (mL/min/kg)*	Serum AUC (mg·h/L)	Reference
7 P healthy; 36 ± 12 y; 7 M	20 mg/kg i.v. lasting 5 min	C_{max} 132 ± 32	2.25 ± 0.74	0.32 ± 0.08*	2.08 ± 0.45*	0→∞ 168 ± 26	77
	40 mg/kg i.v. lasting 5 min	C_{max} 259 ± 32	2.22 ± 0.46	0.36 ± 0.06*	2.31 ± 0.22*	0→∞ 291 ± 25	
9 P with normal renal function; 30 ± 12 y; NR	30 mg/kg i.v. bolus	C_{max} 644	1.91 ± 0.5	21 ± 10	131 ± 53	–	78
6 P with pleural effusion; 54–85 y; 5 M,1 F	30 mg/kg i.v. bolus	C_{max} 350 ± 125	3.27 ± 1.25	16.8 ± 8.4	63.4 ± 11.2	0→∞ 486 ± 38	54
9 P with sepsis; 67 ± 3 y; NR	8 g i.v. lasting 20 min	C_{max} 357 ± 28	3.9 ± 0.9	31.5 ± 4.5	120 ± 22	0→4 h 721 ± 66	49
6 P with extraventricular drainage; 43–61 y; 4 M, 2 F	1 dose 8 g i.v. lasting 30 min	C_{max} 260 ± 85	3.0 ± 1.0	31 ± 10	123 ± 38	0→8 h 929 ± 280	43
	8 g i.v. lasting 30 min tid (steady state)	C_{max} 307 ± 101	4.0 ± 0.5	26 ± 10	83 ± 33	0→8 h 1035 ± 383	
12 P with abscess; 50 ± 16; 6 M, 6 F	8 g i.v. lasting 30 min	C_{max} 446 ± 128	3.7 ± 2.2	28.6 ± 9.9	126 ± 68	0→∞ 1330 ± 609	79

Abbreviations: V_D, volume of distribution; AUC, area under the concentration-time curve; P, patients; M, male; F, female; y, years; NR, not reported; i.v., intravenous; tid, three times daily.

Table 2. Results of selected studies presenting fosfomycin distribution in body after intravenous infusion.

Site	Study subjects; age; gender	Dosage	Serum concentration (mg/L)	Site concentration (mg/L)	Site/serum concentration or (site/serum AUC)	Reference
Lung, normal tissue	8 P pulmonary wedge resection; 26–80 y; 5 M, 3 F	4 g i.v. lasting 30 min	C_{max} 243 ± 58	C_{max} 131 ± 110	(0.55)	52
Lung, infected tissue				C_{max} 107 ± 60	(0.41)	
Pleural effusion	6 P transudative effusion; 54–85 y; 5 M, 1 F	30 mg/kg i.v. bolus	C_{max} 350 ± 125	C_{max} 43 ± 16	0.12	54
Bronchial secretions	11 P with tracheotomy 24–80 y; NR	4 g i.v. (1 g/hour)	C_{max} 120 ± 36	$C_{30\ min}$ 13 ± 11		
			$C_{120\ min}$ 52 ± 18	$C_{120\ min}$ 7 ± 7	0.13	80
Muscle	9 P with sepsis 54–85 y; NR	8 g i.v. lasting 20 min	C_{max} 357 ± 28	C_{max} 247 ± 38	0.69 (0.70)	49
Aortic valve	36 P with heart surgery; 69 ± 9 y; 21 M, 15 F	5 g i.v. lasting 30 min	C_{max} 204 ± 45	C_{max} 27–77	0.13–0.38	81
Mitral valve				C_{max} 40–69	0.20–0.34	
Abscess fluid	12 P undergoing surgery; 31–81 y; 6 M, 6 F	8 g i.v. lasting 30 min	C_{max} 446 ± 128	C_{max} 64 ± 67	(0.42)*	79
SC tissue fluid (noninflamed)	6 P with uncomplicated cellulitis; 62 ± 4 y; 3 M, 3 F	200 mg/kg i.v./8 h lasting 30 min	C_{max} 344 ± 54	C_{max} 141 ± 69	(0.62)	50
(inflamed)				C_{max} 150 ± 71	(0.72)	
Cancellous bone	20 P with hip replacement; 35–80 y; 7 M, 13 F	4 g i.v. (1 g/hour)	$C_{60\ min}$ 105 ± 12	$C_{60\ min}$ 20 ± 5	60 min: 0.19	82
Cortical bone				$C_{60\ min}$ 13 ± 4	60 min: 0.13	
Cancellous bone	20 P with hip replacement; 68 ± y; 8 M, 12 F	4 g i.v. (1 g/h)	$C_{60–120\ min}$ 78 ± 20	$C_{60–120\ min}$ 18 ± 15	0.23	83
Cortical bone				$C_{60–120\ min}$ 17 ± 12	0.22	
Cerebrospinal fluid	6 P with extraventricular drainage; 43–63 y; 4 M, 2 F	8 g i.v. lasting 30 min	C_{max} 307 ± 101 (steady state)	C_{max} 62 ± 38 (steady state)	(0.28) 0→8 h	43
Cerebrospinal fluid	35 P with CSF drainage	5 g i.v. bolus	C_{max} 260 ± 106	C_{max} 12	(0.09)	84
	5 P with CSF drainage	10 g i.v. bolus	C_{max} 440	C_{max} 18	(0.14)	

Notes: *The concentrations achieved in abscess are dependent on the permeability coefficient of the abscess membrane.
Abbreviations: AUC, area under the concentration-time curve; CSF, cerebrospinal fluid; P, patients; M, male; F, female; y, years; NR, not reported; i.v., intravenous; SC, subcutaneous.

in the range 1000–4000 mg/L within four hours. Elimination is prolonged, with mean concentrations above 128 mg/L for more than 24 hours.[52,53] The concentration achieved in urine is the main criterion for the break points chosen by the Clinical and Laboratory Standards Institute.[58] When fosfomycin is taken with food, the peak urinary concentration is lower and appears later.[59,60]

Most of the unabsorbed fosfomycin is recovered unchanged in feces.[61] This property is exploited in Japan for the treatment of enteritis[62] and hemorrhagic enterocolitis.[63–65] The main pharmacokinetic parameters of fosfomycin trometamine are presented in Table 3.

Pharmacodynamic features

According to Matzi et al[52] fosfomycin shows concentration-dependent bactericidal activity on killing curves. After two hours of exposure to different concentrations of the antibiotic, these authors observed a postantibiotic effect in the range of 3.2–4.7 hours. According to Pfausler et al[43] optimal killing is time-dependent, but requires fosfomycin concentrations at least eight times the minimum inhibitory concentration (MIC) in the medium. In a study in which Gram-negative infected catheters were treated with fosfomycin or other antibiotics alone or in combination, no regimen was able to eliminate the organisms.[66]

Concerning neutrophil function against *Escherichia coli*, it has been shown that fosfomycin increased intracellular bactericidal activity, intracellular calcium concentration, and extracellular reactive oxygen intermediate production, did not affect neutrophil phagocytosis, intracellular reactive oxygen intermediate production, or chemokinesis, and decreased chemotaxis.[67]

In a comparison of the ability of antimicrobial agents to modulate the oxidative burst of polymorphonuclear neutrophils triggered by formylmethionyl-leucyl-phenylalanine, fosfomycin had no effect, while antibiotics of the penicillin class (with a 6-aminopenicillanic acid nucleus) had an inhibitory effect, and antibiotics of the cephalosporin class (with a 7-aminocephalosporanic acid nucleus) and ofloxacin showing an enhancing effect.[68] In another study of the immunomodulatory effects of fosfomycin in experimental human endotoxemia, it was concluded that the protein and mRNA levels of tumor necrosis factor, interleukin-1β, and interleukin-6 were almost identical with or without fosfomycin.[69]

Drug interactions

Absorption of fosfomycin trometamine is decreased by metoclopramide and by drugs that stimulate digestive motility, but is not affected by cimetidine.[61] In healthy volunteers, probenecid lowers the renal clearance of fosfomycin, suggesting the existence of tubular secretion.[70]

Several miscellaneous studies have demonstrated the experimental efficacy of fosfomycin in reducing or preventing ototoxicity and/or nephrotoxicity of

Table 3. Mean pharmacokinetic parameters after oral administration of fosfomycin trometamine.

Reference	Nb	Dose g/P	C_{max} mg/L ± sd	t_{max} hours ± sd	$t_{1/2\beta}$ hours ± sd	AUC_{∞} mg/L·h ± sd	Fu %
53	12 H	3 g	21.8 ± 4.8	2.0 ± 0.6	4.5 ± 2.1	145 ± 40	39 (72 h)
48	5 Y	2 g	18.5 ± 10	1.6 ± 0.2	5.4 ± 2.6	102.8 ± 42	60 (24 h)
	7 E	1.8 g	22 ± 8.7	2.2 ± 0.7	8.3 ± 5.5	221.4 ± 95	27 (24 h)
47	5 H	2 g*	18.5 ± 10	1.6 ± 0.2	5.4 ± 2.6	103 ± 42	58 (24 h)
	7 ri I	1.8 g*	22.0 ± 8.7	2.4 ± 1.4	10.8 ± 4.5	388 ±185	32 (24 h)
	6 ri II	1.7 g*	18.5 ± 10	4.6 ± 1.2	24 ± 12	1270 ± 460	24 (24 h)
	5 ri III	1.8 g*	26.0 ± 10	5.1 ± 1.3	50 ± 13	2110 ± 820	11 (24 h)
	5 ri IV	1.8 g*	35.7 ± 10	7.9 ± 3.8	40 ± 20	2370 ± 860	–
60	10 F	**	22.5 ± 6.0	2.5 ± 1.0	7.3 ± 1.7	228 ± 45	23 (8 h)
	10 AM	**	12.7 ± 6.3	3.9 ± 2.1	10.3 ± 3.5	168 ± 57	16 (8 h)

Notes: *25 mg/kg; **50 mg/kg.
Abbreviations: n, number of patients; H, healthy; Y, young adult (26–33 years); E, elderly adult (65–82 years); ri, renal insufficiency; I (CL_{cr} = 30–80 mL/min); II, CL_{cr} = 10–30 mL/min; III, CL_{cr} = 2–10 mL/min; IV, hemodialysis; F, fasting; AM, after meal; P, patient; C_{max}, maximum plasma drug concentration; t_{max}, time to C_{max}; $t_{1/2\beta}$, plasma elimination half-life; AUC_{∞}, area under plasma concentration-time curve to infinity; Fu, percentage of fosfomycin excreted unchanged in the urine after (time of study in hours).

some drugs, including cyclosporine, cisplatinum, and certain antibiotics, eg, the aminoglycosides,[71,72] vancomycin, polymyxin B, and amphotericin B. This efficacy has also been observed in clinical practice.[73–75] Detailed reviews have been published elsewhere.[30,61] Several hypotheses have been made to explain this protective effect with aminoglycosides, including competition for entry that would prevent accumulation and toxicity[71,72] and stabilization of lysosomal membranes.[76]

Antibacterial Activity

Spectrum of activity

Fosfomycin has a broad spectrum of activity which is interpreted differently according to the break points chosen and the method used for susceptibility testing. Table 4 presents the in vitro activity against the main pathogens of the urinary tract reported in various publications. Table 5 presents the activity against the main pathogens encountered in enteritis. Briefly, fosfomycin is quite effective (MICs < 16 mg/L and less than 10% of resistant strains) against *Staphylococcus aureus*, the main species of *Enterobacteriaceae*, *Aeromonas hydrophila* and *Campylobacter* spp. It is moderately effective (32 ≤ MICs < 128 mg/L and/or >20% of resistant strains) against *Streptococcus* spp, *Enterococcus* spp, many strains of coagulase-negative *Staphylococcus* spp, *Morganella morganii, Providencia* spp, *Vibrio* spp, and *Pseudomonas aeruginosa*. It is almost ineffective (MICs > 128 mg/L and/or >50% of resistant strains) against *Staphylococcus saprophyticus, Corynebacterium* spp, *Mycobacterium* spp, *Bordetella* spp, *Borrelia* spp, *Legionella* spp, *Burkholderia cepacia, Stenotrophomonas maltophilia, Acinetobacter* spp, *Bacteroides* spp, *Chlamydia* spp, *Mycoplasma* spp, and *Ureaplasma urealyticum.*

Mechanism of action

Classically, fosfomycin enters bacterial cells by two active pathways, ie, the glycerophosphate transport system which is partly constitutive but antagonized by the phosphate ion, and by the hexose phosphate

Table 4. Antibacterial activity of fosfomycin against the main urinary pathogens.

Species	M	N	MIC range	MIC_{50}	MIC_{90}	% R > 32 mg/L	% R ≥ 256 mg/L	Reference
Escherichia coli	A	1097	0.1–64	0.5	1.0	<0.1	<0.1	160
	A	315	1–128	2	8		2.2	36
	B	139	0.5–512	1	4	0.7	0.7	161
Klebsiella spp.	A	184	1–512	16	64	14	9	134
Klebsiella pneumoniae	A	14	8–128	32	>128		29	36
	B	40	16–512	32	64	27	10	162
Klebsiella oxytoca	B	44	4–512	16	32	4.5	4.5	162
Enterobacter spp.	A	172	0.5–512	16	256	28	3	134
	A	45	1–256	16	32			87
	B	45	≤1–512	32	128		7	87
Enterobacter cloacae	A	28	<0.1–6.2	1.6	3.1			163
	B	16	16–256	64	128	56	6.2	164
Enterobacter aerogenes	A	28	0.1–6.2	0.8	1.6			163
	B	44	8–64	32	64	39	4.5	165
Serratia marcescens	A	21	0.1–12	0.2	1.6			163
	B	77	16–256	64	128	71	5.2	166
Citrobacter spp.	A	30	2–8	2	4		0	87
Proteus mirabilis	A	42	≤1–128	4	>128		19	36
Proteus vulgaris	A	10	≤1–128	16	>128		40	36
Morganella morganii	A	39	128–128	32	128		4.9	36
Providencia spp.	B	116	4–512	128	512	66	48	167
Pseudomonas aeruginosa	A	182	1–512	16	256	26	10	134
Enterococcus spp.	A	157	16–128	32	64	25	2.5	160
Staphylococcus aureus	B	148	<0.5–64	2	4			168
Staphylococcus saprophyticus	B	30	16–512	64	512		20	87

Abbreviations: M, method for MIC determination (A, agar, B, broth); N, number of strains; MIC, range in mg/L; MIC_{50} or MIC_{90}, MIC necessary to inhibit 50% or 90% strains, respectively; % R, percentage of strains resistant with MIC > 32 mg/L (European Committee on Antimicrobial Susceptibility Testing) or ≥256 mg/L (Clinical and Laboratory Standards Institute).

Table 5. Antibacterial activity of fosfomycin against the main agents of enteritis.

Species	M	N	MIC range	MIC_{50}	MIC_{90}	% R > 32 mg/L	% R ≥ 256 mg/L	Reference
E. coli STEC	A	129	0.5–512	8	32			169
E. coli O157	B	43	0.1–0.5	0.5	0.5	0	0	141
E. coli non-O157	B	56	1–64	4	16		0	141
Shigella spp.	A	11	0.2–0.8	0.4	0.8			163
Shigella spp.	B	73	0.3–512	2	16	8.2	8.2	161
Salmonella spp.	A	17	0.2–6.2	0.4	0.8			163
Salmonella spp.	B	68	0.2–128	0.5	4	1.5	0	170
Salmonella Typhi	B	15	32–256	128	256	93	27	170
Salmonella Paratyphi A	B	6	256–512	256	512	100	100	170
Yersinia enterocolitica	B	152	0.1–256	0.5	32	5.9	0	171

Abbreviations: M, method for MIC determination (A agar, B broth); N, number of strains; MIC range in mg/L; MIC_{50} or MIC_{90}, MIC necessary to inhibit 50% or 90% strains, respectively; % R, percentage of resistant strains with MIC > 32 mg/L (European Committee on Antimicrobial Susceptibility Testing) or ≥256 mg/L (Clinical and Laboratory Standards Institute).

uptake system that is inducible (ie, not expressed in the absence of a competent inducer, eg, glucose-6-phosphate). The glycerophosphate transport system is widespread in the bacterial world, while the hexose phosphate uptake system is confined to *Staphylococcus* spp and *Enterobacteriaceae* (with the exception of *Proteus* spp).[85–87]

Once inside the cell, fosfomycin acts as an analog of phosphoenolpyruvate and inhibits enolpyruvyl transferase (also known as MurA), a cytoplasmic enzyme that allows the first step of synthesis of N-acetylmuramic acid.[86,88–91] Because N-acetylmuramic acid is a major component of glycan strands in the cell wall, fosfomycin blocks cell wall synthesis with a lethal effect.[86,92,93]

Mechanisms of resistance

In spite of the broad spectrum of fosfomycin antibacterial activity, several species are naturally resistant and in some of these the mechanism of resistance has been identified. The resistance of enolpyruvyl transferase to inactivation by fosfomycin was demonstrated in *Mycobacterium tuberculosis*,[94] *Vibrio fisheri*,[95] and *Chlamydia trachomatis*.[91]

In susceptible organisms, several mutations in *murA* demonstrate a lower affinity of its product to phosphoenolpyruvate and may lead to fosfomycin resistance[96–98] associated with a lower rate of peptidoglycan synthesis.[98] However, resistance to fosfomycin due to overexpression of enolpyruvyl transferase has been also observed.[96]

Several modifying enzymes have been described, sometimes in species that could produce this antibiotic,[99] but also in strains that harbor plasmidic or chromosomal resistance. In all cases, they lead to the formation of inactive adducts:

- FosA is a metalloenzyme. It opens the epoxide ring of fosfomycin and forms a covalent bond between the sulfhydryl residue of the cysteine in glutathione and the C-1 of fosfomycin.[100–102] This type of resistance has been found in some Gram-negative strains (*Enterobacteriaceae, Pseudomonas* spp, and *Acinetobacter* spp),[103] where it is either encoded by plasmids or by the chromosome.[104] It is worth underlining the important similarities between the DNA of these genes and those of several strains of *Streptomyces* spp.[99]
- FosB allows the formation of L-cysteine-fosfomycin. This type of resistance has been found in Gram-positive species only, either encoded by plasmids in *Staphylococcus* spp,[103,105,106] or by the chromosome in *Bacillus subtilis*.[107] Because the amino acid sequence of FosB is 48% identical to that of FosA, a common origin is likely.[106,107]
- FosC allows fosfomycin phosphorylation with ATP as a cosubstrate. It has been described in *P. syringae*, a species that naturally produces fosfomycin.[29] A similar mechanism has been described with *fomA* and *fomB* in *Streptomyces wedmorensis*,[108] and with rare strains of *P. aeruginosa*.[109]
- FosX leads to a water adduct. It has been described in *Mesorhizobium loti* and *Listeria monocytogenes*.[110–112]

Mutations in transport systems (*glpT* or *uhpT*) are easily observed in laboratory studies, and lead to a

decrease in uptake of the drug, and thus resistance to fosfomycin.[85,86,113,114] They may be associated with mutations in their regulatory genes, such as *uhpA* (encoding a regulator protein required for activation of the *uhpT* promoter), or *ptsI* and *cyaA*, the products of which are involved in the synthesis of cyclic AMP and therefore regulate the level of glycerophosphate transport.[96,114–116]

Although many mechanisms of resistance to fosfomycin have been described since its discovery, mutations of fecal *E. coli* strains during treatment of uncomplicated acute cystitis do not appear to be clinically relevant, which sets them apart from the fluoroquinolones.[117] For some authors, the observation that fosfomycin resistance does not increase with the passage of time could be due to the fact that mutations in *murA* and in transport systems have a biological cost which is not compatible with their persistence in the community.[114,118,119] But another concern about the lack of development of fosfomycin resistance must be considered, ie, that it has been little used in the past, either in human or animal therapies.[120]

Considering the present status of its susceptibility, fosfomycin often appears to be an interesting therapeutic option for the treatment of multidrug-resistant *Enterobacteriaceae*,[9,12,17,21,23,40,121–123] but there have been a few reports that sound a note of caution. In some, fosfomycin resistance is encoded by a gene included in a transposon[124,125] or by gene cassettes included in integrons,[126–128] and we know that sometimes such resistance may be responsible for outbreaks of multidrug-resistant infections that are difficult to treat.[38,129] In a study describing the trends for fosfomycin resistance in strains of *E. coli* producing CTX-M-15 extended-spectrum β-lactamase, Oteo et al[128] reported an increase in fosfomycin resistance from 3% in 2003–2004 to 21% in 2008, during which time fosfomycin use increased by 50%.

In vitro susceptibility testing and interpretative standards

Susceptibility testing for fosfomycin may be performed by the agar disk diffusion method, the gradient diffusion method (Etest®, AB Biodisk, Solna, Sweden), the agar or broth dilution method, or by the break point dilution method. Unfortunately, for many reasons, fosfomycin susceptibility results were not reported in many of the publications dealing with multidrug-resistant bacteria.[130–132]

The results of in vitro susceptibility testing may be influenced by many factors. In particular, phosphate ions are able to inhibit the glycerophosphate transport system, while a high concentration of dextrose represses the hexose phosphate uptake system, therefore false resistant results may be reported if the medium does not include an inducer for the hexose phosphate uptake system.[86,93,133] In correct for this, the practice of adding glucose-6-phosphate to Mueller Hinton medium was generally adopted. For practical purposes, this may be achieved either by adding glucose-6-phosphate 25 mg/L to the agar for MIC determinations, or by loading fosfomycin susceptibility discs with glucose-6-phosphate 50 µg.[133,134] The antibacterial activity of fosfomycin is enhanced when pH decreases from 7.9 to 5.5[133] and in an anaerobic atmosphere.[135–137]

Probably because mutations are better expressed in a liquid medium, MIC determinations in broth were thought to be too high compared with agar determinations,[138] but it is possible to find good agreement between broth and agar determinations if a faint haze of growth is ignored in a liquid medium.[87] MIC determinations may be equally influenced by the size of the inoculum or the way it was prepared.[93]

The clinical significance of the role of glucose-6-phosphate in penetration of the bacterial cell by fosfomycin has been debated because glucose-6-phosphate is known to be absent in sterile urine,[139] in normal cerebrospinal fluid,[140] and in the intestine,[141] but it is present in normal serum at a concentration of 4 ± 1 mg/L,[141] and in lysed red blood cells at a concentration of 3.9–7.8 mg/L.[86] Therefore, glucose-6-phosphate must be considered to be a potential inducer of fosfomycin uptake at infection sites if there is an effusion of serum or red blood cells. In contrast, urine is normally the physiological elimination route for phosphate ions that are not incorporated into bone. The amount of phosphorus eliminated may vary from 1 g to 5 g per day, and this may inhibit the entry of fosfomycin into bacterial cells which naturally lack the hexose phosphate uptake system.

Generally, there is a good correlation between disc susceptibility tests and MICs, but some discrepancies have been observed with *Klebsiella*

pneumoniae strains, especially when extended-spectrum β-lactamase-producing strains were assessed, even with Etest determinations.[9,142,143] This observation is of concern because meaningful evaluation of clinical studies requires accurate data on in vitro susceptibility.

According to the Clinical and Laboratory Standards Institute, taking into account the concentrations observed in urine after a single oral dose of fosfomycin trometamol, a strain is considered as susceptible, intermediate, or resistant if its MIC is ≤ 64, =128, or ≥256 mg/L, respectively.[58] When considering blood and tissue concentrations observed after intravenous administration, according to the European Committee on Antimicrobial Susceptibility Testing, a strain is considered susceptible if its MIC is ≤ 32mg/L and is considered resistant if its MIC is > 32mg/L.[144] The same break points are used for oral administration of the drug.

Activity against multidrug-resistant strains of *Enterobacteriaceae*

Because bacterial resistance to fosfomycin is rarely observed in outbreaks of multidrug resistance, its activity against various pathogens has been extensively studied in the last decade. The results of a few such studies are presented in Table 6. In several of these, the number of strains observed is limited, so they have no true statistical value because some isolates might be genetically related.[145]

In vitro synergism

As a consequence of the occurrence of resistant mutants during treatment, it was difficult to use fosfomycin as a single agent,[32] so combinations with other antibiotics were soon considered, especially for the treatment of multiresistant strains.[146–150] In studies that considered the effect of a combination of fosfomycin with cefotaxime, ceftriaxone, ceftazidime, or aztreonam against a series of strains with known patterns of resistance, a synergistic effect (fractional inhibitory concentration [FIC] index ≤0.5) was observed with more than 50% of strains of *Enterobacteriaceae* when they produced a cephalosporinase (*E. coli, Enterobacter cloacae, Serratia marcescens, Serratia liquefaciens*, and *Proteus vulgaris*),[151,152] excepted *M. morganii* and *Providencia stuartii*,[152] while the effect was mostly

Table 6. Fosfomycin in vitro activity against multidrug-resistant *Enterobacteriaceae.*

Species	Mechanism of resistance	Number of strains (country)	% Fos S or (% Fos R)	Reference
Escherichia coli	MDR	315 (Sp)	97.2	36
	ESBL	90 (Au)	97	12
	ESBL	178 (UK)	95.2	121
	MDR	26 (Gr)	100	172
	CTX-M-15	98 (Sp)	(15.3 R)	173
	CTX-M-14	54 (Sp)	(5.3 R)	173
	SHV-12	23 (Sp)	(5.1 R)	173
	ESBL	71 (Sp)	94.4	16
	CTX-M	46 (USA)	91.3	17
	ESBL	132 (Tk)	100	174
	ESBL	89 (HK)	(1.1 R)	175
	ESBL	161 (Sp)	99	122
Klebsiella pneumoniae	bla_{KPC}	68 (USA)	93	9
	MDR	116 (Gr)	90.5	172
	M-BL	21 (Gr)	81.0	172
	Carbapenemase	74 (Gr)	94.6	172
	KPC-2	50 (Gr)	54	42
	ESBL	13 (Sp)	0	16
Klebsiella spp.	MDR	14 (Sp)	71.4	36
Klebsiella spp.	ESBL	44 (Tk)	(4.5 R)	174
Proteus mirabilis	MDR	7 (Gr)	100	172
Proteus mirabilis	MDR	42 (Sp)	73.8	36
Enterobacter spp.	MDR	42 (Sp)	82.9	36

Abbreviations: MDR, multidrug resistant (resistant to at least three classes of antibiotics); ESBL, extended spectrum β-lactamase; M-BL, metallo-β lactamase; Au, Austria; Gr, Greece; HK, Hong Kong (China); Sp, Spain; Tk, Turkey; UK, United Kingdom; USA, United States of America.

additive (1 ≥ FIC index > 0.5) against strains that produced a penicillinase (*E. coli, K. pneumoniae*, and *Proteus mirabilis*).[152] This kind of combination was successfully used for parenteral treatment of a few severe infections in critically ill patients, mainly due to Staphylococci,[153–156] but sometimes due to resistant *Enterobacteriaceae*.[45] Few other data are available on multiresistant strains of *Enterobacteriaceae*.[157] A synergistic effect of fosfomycin against *S. marcescens* was observed when combined with mezlocillin, cefoxitin, gentamicin, or nalidixic acid,[150] or when combined with tazobactam/piperacillin.[158]

In a study in rabbits of experimental endocarditis caused by a strain of *K. pneumoniae* producing a TEM-3 beta-lactamase and treated with fosfomycin + gentamicin combination, this combination appeared active while fosfomycin alone was not, gentamicin alone was active only in a high-dose regimen, and in vitro combination was additive only (FIC index = 0.75).[146]

Netikul et al[159] pointed out that combination of fosfomycin with carbapenems was not synergistic (0.75 ≤ FIC index ≤ 2.0) against strains of *E. coli* or *K. pneumoniae* with decreased susceptibility to at least one carbapenem. In this study, the combination was assessed with the Etest, even though the Etest do not give reliable results for determination of the fosfomycin MIC in extended-spectrum β-lactamase-producing strains of *K. pneumoniae*.[9,142,143]

With regard to multiresistant *Enterobacteriaceae*, there is a need for additional research because, in the event that a new extended-spectrum β-lactamase appears, the right partner for fosfomycin needs to be identified.

Drug Administration and Dosage

Intravenous administration

In severe infections in adults or children, the dose of fosfomycin administered is currently 100–200 mg/kg/day in 2–3 infusions per day. It may be doubled for a period in the treatment of central nervous system infections. Because fosfomycin 1 g provides 14.4 mEq of sodium, 5% glucose solutions should be used instead of saline solutions. Slow infusions over four hours are preferred because the drug concentration remains at a therapeutic level for a longer time, but infusions lasting a few minutes may be used, but with a risk of hypokalemia.[176]

Few data are available in neonates.[153,154,177,178] In a study performed in 10 neonates receiving 100 mg/kg intravenously twice a day, fosfomycin concentrations exceeded the MICs for most pathogens for over 12 hours after infusion, and the main pharmacokinetic parameters (peak plasma concentration, AUC, and half-life) were not significantly different between 30-minute or two-hour infusions.[179]

In the event of renal impairment, no dose reduction is needed if creatinine clearance is above 60 mL/min. Below this value, the same dose is administered with a longer period between infusions, ie, 12 hours for 60 > creatinine clearance ≥40, 24 hours for 40 > creatinine clearance ≥30, 36 hours for 30 > creatinine clearance ≥20; 48 hours for 20 > creatinine clearance ≥10 mL/min.

Because fosfomycin is removed by hemodialysis, Bouchet et al[180] suggested administering 2 g intravenously after each dialysis session. During venovenous hemofiltration, Gattringer et al[181] proposed administering 8 g every 12 hours. In peritoneal dialysis, Bouchet et al[182] observed therapeutic serum concentrations after 1 g administered intraperitoneally every 48 hours in anuric patients, or every 36 hours in patients with residual renal function.

Oral administration

A single dose of 3 g is currently used for the treatment of uncomplicated urinary tract infections. A 2 g dose has been proposed for the treatment of children, but this dose strength is not available everywhere.[183] In complicated urinary tract infections, when a longer duration of treatment is needed, some authors have proposed repeating three times the 3 g dose every other day.[184,185] In cases of renal impairment, the dose does not need to be reduced.[48]

Clinical Studies

Given the pharmacokinetic features and broad-spectrum antibacterial activity of fosfomycin trometamine, a single dose can be proposed for the treatment of uncomplicated lower urinary tract infections. Its efficacy in this condition has been assessed by many studies and has been reviewed by several authors.[55,186,187] The studies were nonblinded, single-blinded, or double-blinded comparisons. A single 3 g dose of fosfomycin

was compared with single doses of amoxicillin 3 g,[188,189] ofloxacin 200 mg,[190] norfloxacin 800 mg,[191] pefloxacin 800 mg,[192] trimethoprim 200 mg,[193] and cotrimoxazole 1920 mg.[190] A single dose of fosfomycin was also compared with amoxicillin + clavulanic acid 375 mg four times daily for five days,[194] cefalexin 500 mg four times daily for five days,[195] ciprofloxacin 500 mg twice daily for five days,[196] pipemidic acid 400 mg twice daily for 5–7 days,[197–199] norfloxacin 400 mg bid for 5–7 days,[197,200–203] cotrimoxazole 480 mg twice daily for three days,[204] trimethoprim 200 mg twice daily for five days,[18] and nitrofurantoin 50 mg four times daily for seven days.[205] In these studies, the microbiological and clinical efficacies were similar, and 70%–95% microbial eradication rates were observed 5–11 days after treatment.

Fosfomycin trometamine has also been investigated in pregnancy. In early studies, it was compared with nitrofurantoin and pipemidic acid in the treatment of lower urinary tract infections.[55,199] More recently, it has been compared with ceftibuten 400 mg once daily for three days, with a 95% therapeutic success rate (clinical cure and bacteriological eradication).[206] In the treatment of asymptomatic bacteriuria, a single dose of fosfomycin trometamine showed the same level of therapeutic success as cefuroxime axetyl for five days (93.2% versus 95%),[207] and as amoxicillin + clavulanic acid for seven days (eradication rate over 80% in both groups).[208]

A single 2 g dose of fosfomycin trometamine was also compared with pipemidic acid 200 mg twice daily for seven days in children weighing more than 25 kg.[183] Bacteriological results showed that at the end of follow-up (one month), urine was sterile in 70.8% and 70.3%, respectively, and the difference was not statistically significant.

Few data are available on the efficacy of intravenous fosfomycin as a single agent,[32,209,210] although this has been used widely in combination regimens to treat severe infections, mostly with beta-lactam antibiotics. Recent publications have demonstrated its activity as second-line treatment in limb-threatening diabetic foot infections,[211] and in pneumonia due to carbapenem-resistant *P. aeruginosa*.[212]

Multidrug-resistant *Enterobacteriaceae*

As a consequence of advancing drug resistance in common bacterial urinary pathogens and in the absence of new antimicrobial agents to treat them, a re-evaluation of fosfomycin has been undertaken by many investigators.[15,19–24,213] Few new data are available as yet, but because fosfomycin is generally not affected by multidrug resistance, the old publications could offer some confidence in its efficacy while we await the results of ongoing studies.

Table 7 presents the latest clinical results for multidrug-resistant *Enterobacteriaceae*. Senol et al[184] compared the efficacy of fosfomycin (three 3 g doses being taken orally, every other night) with that of a carbapenem, either imipenem cilastatin (0.5 g intravenously four times daily for 14 days) or meropenem (1 g intravenously three times daily for 14 days) in complicated urinary tract infections. Clinical and microbiological outcomes were similar in both groups, but the drug acquisition costs were very different. In the study by Rodriguez-Baño et al[214] one 3 g dose of fosfomycin trometamine was compared with amoxicillin + clavulanate (500/125 mg three times daily for 5–7 days), the overall cure rate was the same, but in the amoxicillin + clavulanate group, there was a significant difference ($P = 0.02$) according to the susceptibility level of the extended-spectrum β-lactamase strains of *E. coli* to amoxicillin and clavulanate, ie, with an MIC $\leq$ 8 mg/L, 26 of 28 patients were cured (92.8%), while with MIC $\geq$ 16 mg/L, only five of nine patients were cured (55.5%). Although the study by Pullucku et al[185] was not randomized or controlled, its results sparked interest in fosfomycin trometamine with regard to extended-spectrum β-lactamase-producing *E. coli* in urinary tract infections with or without complicating factors.

The background to the study by Michalopoulos et al[215] was very different because it demonstrated interest in the use of intravenous fosfomycin in combination with other antibiotics for severe infections with extensively resistant strains of *K. pneumoniae*. The bacteriological and clinical outcomes in all 11 patients were good, and all-cause mortality was 18.2%.

A case report on gastroenteritis due to a multidrug-resistant strain of *Salmonella typhimurium* was reported as showing a complete response to fosfomycin,[216] but it is not possible to draw a conclusion or make a recommendation on the basis of a case report.

Table 7. Clinical studies on fosfomycin for the treatment of multidrug-resistant *Enterobacteriaceae* infections.

Study design; country; period; reference	Type of infection	Patient characteristics (gender, age, CF)	Underlying conditions	Causative agent	Treatment	Outcome success/inclusion
Prospective; Turkey; March 2005–January 2006; 184	Complicated UTI	13 M, 14 F 57 ± 15 y 1.7 ± 0.5 7 M, 13 F 57 ± 21 y 1.8 ± 0.7	Various urological or neurological risk factors	*E. coli* ESBL	FT 3 g po/2 d × 3 8 Ipm 0.5 g iv qid × 14 d 12 Mer 1 g iv tid × 14 d	21/27 19/20*
Prospective; Spain; February 2002–May 2003; 214	Community-acquired cystitis	Outpatients 28 Outpatients 37	Risk factors reported for the whole cohort (n = 112)	*E. coli* ESBL (Fos S)	FT 3 g (1 dose) AMC po 500/125 mg tid × 5–7 d	26/28 31/37**
Retrospective; Turkey; September 2004–July 2006; 185	UTI Uncomplicated (n = 16), Complicated (n = 42)	52 inpatients or outpatients 55 ± 18 y 25 M, 27 F	±Various urological or neurological risk factors	*E. coli* ESBL Fos S but Cip + Sxt R	FT 3 g, 2 d × 3	49/52
Prospective; Greece; May 1–December 15, 2008; 215	Severe infections in ICU	Inpatients 5 M, 6 F 67 ± 14	Mechanical ventilation + various risk factors	*K. pneumoniae* MDR and carbapenem-resistant	4 g Fos Na iv qid*** combined according to susceptibility	11/11
Case report Japan; September 2000; 216	Acute gastroenteritis	Inpatient male infant 35 days old	None	*Salmonella typhimurium* MDR	Fos Na iv (dose NR)	Cure

Notes: *20 patients treated with a carbapenem, 8 with imipenem and 12 with meropenem; **cure rate = 17/18 strains when AMC MIC ≤ 4 mg/L, 9/10 when AMC MIC = 8 mg/L and 5/9 when AMC MIC ≥ 16 mg/L; ***dose reduced to 2 g four times daily in the elderly or if renal impairment, combinations with colistin (n = 6), gentamicin (n = 3), piperacillin + tazobactam (n = 1).
Abbreviations: UTI, urinary tract infection; ICU, intensive care unit; CF, number of complicating factors; M, male; F, female; ESBL, extended spectrum β-lactamase; MDR, multidrug resistant; FT, fosfomycin trometamine; Ipm, imipenem; Mer, meropenem; AMC, amoxicilline + clavulanic acid; Fos Na, sodium salt of fosfomycin; po, per os; iv, intravenous; /2 d: once every other day; qid, four times daily; tid, three times daily; NR, not reported.

Toxicity and Safety

The toxicity of both orally and intravenously administered fosfomycin is low. In comparative studies, drug-related adverse events were reported in >1% of the treated populations, ie, diarrhea 9.0%, vaginitis 5.5%, nausea 4.1%, headache 3.9%, dizziness 1.3%, asthenia 1.1%, and dyspepsia 1.1%.[217] Only diarrhea appeared more frequently in patients treated with fosfomycin than in those treated with nitrofurantoin, cotrimoxazole, or ciprofloxacin, but a new evaluation would be necessary now because the study was performed with the calcium salt of fosfomycin. For the other parameters, fosfomycin demonstrated rather fewer side effects. Adverse events with fosfomycin were usually mild and transient, lasting for a mean of 1.8 days.[55,198,201] No fetal toxicity was reported.

The allergic risk is low. A single case report of anaphylactic shock was reported,[217] along with a single case report of liver toxicity during coadministration with imipenem (3 g daily) and parenteral nutrition with lipids and fosfomycin (12 g daily) in a female patient with cystic fibrosis.[61,218]

In a retrospective study of 72 intravenous fosfomycin courses, Florent et al[176] observed a 26% rate of hypokalemia, which was attributed to the 30–60-minute infusion and was not observed with the four-hour protocol. The mechanism involved might be distal tubular excretion of potassium with high doses of fosfomycin.

Patient Preference

Uncomplicated urinary tract infections are frequently observed in clinical practice. They are often treated without documentation but with a high probability of success. With the development of resistance, commonly used antibiotics, eg, amoxicillin, cotrimoxazole, and the quinolones, are showing decreasing activity, particularly since new mechanisms of resistance have been detected in the community.[12–14,219] This resistance may be observed also in veterinary practice,[220] in sewage sludge and liquid pig manure,[221] and in cow excrement.[222] Given that the choice of a first-line treatment for uncomplicated urinary tract infection must be made according to the probability of success/failure, the likelihood of adverse effects, and cost considerations, fosfomycin appears to be a convenient option at the present time.

The risk factors for acquisition of multidrug-resistant *Enterobacteriaceae* were defined a few years ago, ie, age over 50–65 years,[5,39,175,214,219] admission from a nursing home,[175,214,223] and previous antimicrobial therapy.[3,7,37,175,223] When these risk factors or complications are observed, documentation of infection is needed, and the choice of antibiotic therapy is made according to susceptibility, but fosfomycin appears to be an important agent for the treatment of such infections.

Conclusion

The dramatic increase in antimicrobial resistance of *Enterobacteriaceae* is of worldwide concern, with the frequent problem of extensively resistant strains. This situation has led to the search for alternative agents able to treat infections caused by these organisms. Some authors have proposed fosfomycin, an antibacterial agent that has shown very good activity against most strains of *Enterobacteriaceae*.

In uncomplicated urinary tract infections, a single oral dose is safe and effective, especially when multidrug-resistant strains are concerned. In complicated urinary tract infections, the same results can be achieved with several doses. In both situations, fosfomycin could be an interesting therapeutic option in that it limits the use of carbapenems for treating infections that could be cured at a lower cost, without increasing the risk of resistance. In severe infections, combinations with intravenous fosfomycin have proved to be effective in the past, but their future activity needs to be clarified because it depends on choosing the right partner drug. In any case, given the fast evolution of resistance, more studies are urgently needed.

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Disclosure

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