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Current key topics in fosfomycin

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New perspectives for reassessing fosfomycin: applicability in current clinical practice

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ABSTRACT

Fosfomycin is a bactericidal antibiotic that interferes with cell wall synthesis. The drug therefore has a broad spectrum of activity against a wide range of Gram-positive and Gram-negative bacteria. Both the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) have started review processes of the accumulated information on the use of fosfomycin and on information from new clinical trials. The intent is to establish usage terms in Europe and to authorize the sale of fosfomycin in the US. This monograph reviews the most current aspects of the compound. From the microbiological point of view, fosfomycin's single mechanism of action can provide a synergistic effect to other classes of antibiotics, including β-lactams, aminoglycosides, lipopeptides and fluoroquinolones. The resistance mechanisms include the reduced intracellular transport of the antibiotic, the change in target and the direct inactivation of the antibiotic by metalloenzymes and kinases; however, the clinical impact of some of these mechanisms has not yet been elucidated. The lack of agreement in determining the sensitivity cutoffs between the Clinical and Laboratory Standards Institute (CLSI) (≤64 mg/L) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (≤32 mg/L), the fact that a number of microorganisms require a higher MIC (*Klebsiella* spp., *Enterobacter* spp., *Serratia* spp., *Pseudomonas aeruginosa*) and the drug's different effective concentrations against Gram-positive and Gram-negative bacteria have resulted in recommended dosages for treating multiresistant microorganism infections that vary between 8 and 12 g/day for Gram-positive bacteria and 16 and 24 g/day for Gram-negative bacteria. Fosfomycin has 3 presentations (intravenous with disodium salt, oral with calcium salt and combined with tromethamine), has good distribution in tissues and abscesses and is well tolerated. The pharmacodynamic ratio of dosage production for fosfomycin is AUC/MIC. However, the pharmacokinetics/pharmacodynamic ratio could be optimized in daily practice based on the pathogen, the patient's clinical profile or the infection model. Fosfomycin is the treatment of choice for cystitis in immunocompetent patients, patients with transplants, pregnant women and in pediatric settings. The drug is especially useful due to its microbiological activity and oral posology in cystitis caused by ESBL bacteria. Administer intravenously at high doses and combined with other antimicrobial agents. Fosfomycin has been useful in treating infections by multiresistant Gram-negative bacteria, such as *Enterobacteriaceae*, carbapenemase carriers and *P. aeruginosa*, extensively resistant or panresistant in urinary infections and in skin and soft tissue. Fosfomycin has also been shown active in combination with daptomycin or imipenem in osteoarticular infections by methicillin-resistant *Staphylococcus aureus*. Fosfomycin is an old antibiotic that still has much to reveal.

Key-words: Fosfomycin, resistance, pharmacodynamic, treatment, multiresistant microorganisms

BACKGROUND

Fosfomycin was discovered and synthesized in the Medina Foundation (Fundación Medina, Granada, Spain) from *Streptomyces fradiae* and *Pseudomonas syringae*. The drug acts by inhibiting UDP-N-acetylglucosamine enolpyruvyl transferase (MurA), an enzyme responsible for catalyzing the formation of N-acetylmuramic acid, a precursor of peptidoglycan, through the binding of N-acetylglucosamine and phosphoenolpyruvate, resulting in bacterial lysis (figure 1). Gram-positive and Gram-negative bacteria require the formation of N-acetylmuramic acid for peptidoglycan synthesis, which means that fosfomycin's spectrum of action is very broad, presenting activity against the main genera in clinical practice, such as *Staphylococcus* spp., *Enterococcus* spp., *Enterobacteriaceae*,

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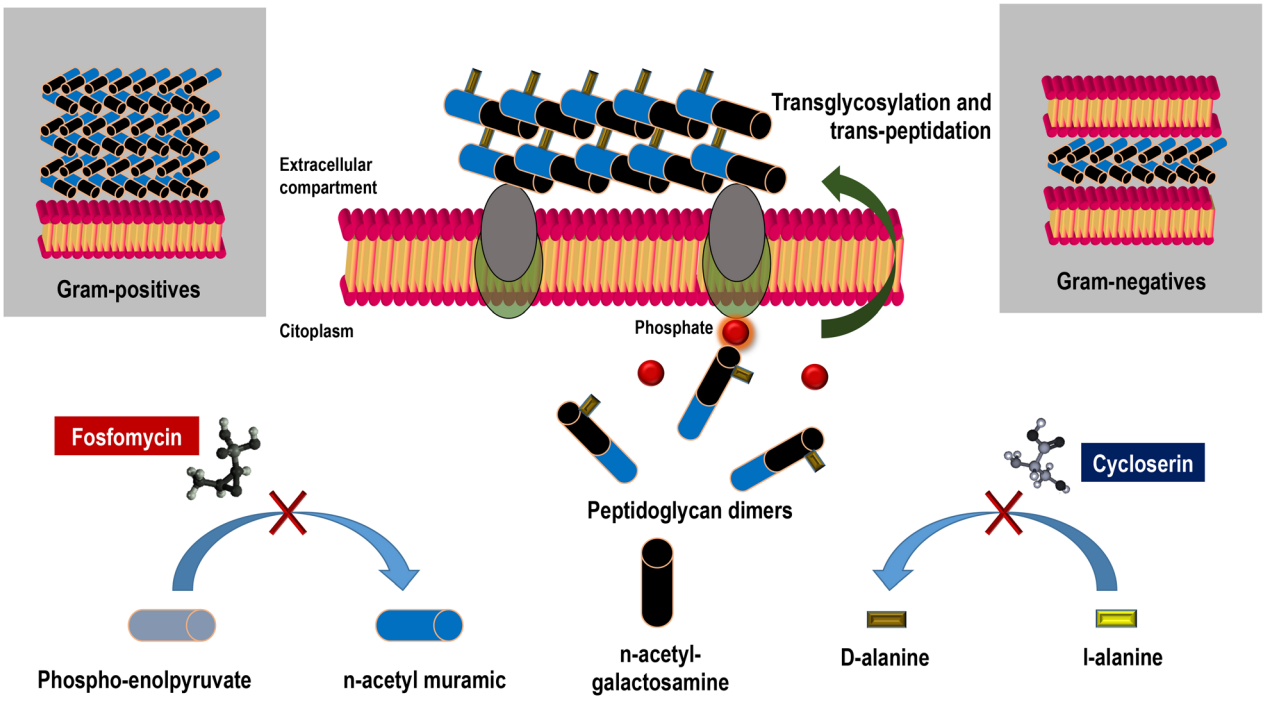

Figure 1 | **Mechanism of action of fosfomycin. Impact on synthesis of bacterial wall**

Pseudomonas spp. and *Acinetobacter* spp. Fosfomycin is water-soluble, has a low molecular weight (138 g/mol) and has low protein binding, which provides it with high tissue dissemination (volume of distribution of 0.3 L/kg). Fosfomycin also disseminates in experimental biofilm models in concentrations greater than or equal to those of ciprofloxacin and cotrimoxazole [1].

Both the European Medicines Agency and the US Food and Drug Administration have started reviewing the accumulated information on the use of fosfomycin and the information from new clinical trials. The intent is to establish common usage criteria in Europe and to authorize the sale of fosfomycin in the US [2, 3]. In its various formulations (both intravenous [disodium salt] and oral [calcium salt or trometamol]), the prescription of fosfomycin has increased spectacularly due to the considerable incidence of multidrug-resistant microorganisms in which fosfomycin constitutes, alone or in combination, a treatment option [4, 5].

NEW MICROBIOLOGICAL DATA

Fosfomycin's mechanisms of resistance include the reduction in intracellular transport of the antibiotic (mutation in transporter genes, regulator genes or ampC for *glpT*), the change in target due to changes in the expression of *murA* and the direct inactivation of the antibiotic by metalloenzymes (*fosA*, *fosB* and *fosX*) or by kinases (*formA* and *formB*) [6].

Despite the considerable ease of selecting fosfomycin-resistant mutations, their clinical repercussion has not been sufficiently tested. In some cases, resistance reduces the bacteria's fitness; in others, resistance reduces its virulent nature (such as its ability to adhere to epithelial cells and synthetic materials such as catheters) [7, 8]. A more limiting aspect is the mechanism of direct inactivation of the antibiotic by metalloenzymes (FosA, FosB and FosX), which are transmissible and frequently found in ESBL enterobacteria and carriers of carbapenemases, especially *Escherichia coli* [9].

There have been recent reports of the presence of mutations with a loss of *uhp*T expression, which phenotypically cause the growth of *E. coli* colonies in the halo of inhibition, with no correlation with the symptoms [10]. Given that the rate of concentration of mutations depends on the concentration of fosfomycin being above the microorganism's minimum inhibitory concentration (MIC) (1 of every $5.5x10^5$ with concentrations 5 times the MIC and $1.2x10^9$ with concentrations 256 times the MIC), this resistant mutant selection window can be prevented with high doses of the drug, especially if prescribed in monotherapy [11]. A recent meta-analysis [12] found a 3.4% (95% CI 1.8-5.1%) rate of resistances in treatments with fosfomycin in monotherapy, which, coupled with the synergistic activity with other antimicrobials, establishes attractive prescription scenarios, such as the therapeutic combination against multidrug-resistant microorganisms.

The aforementioned meta-analysis established the ben-

efit of employing fosfomycin in combination with another antibiotic over monotherapy. In an extensive review, Falagas et al. described fosfomycin's synergistic in vitro effect, combined with any antimicrobial, against sensitive and resistant Gram-positive and Gram-negative microorganisms [4]. The combination of fosfomycin and meropenem is synergistic and prevents the onset of drug resistance in severe infections caused by strains of ESBL-producing enterobacteria and *P. aeruginosa* [13]. The combination of fosfomycin and tobramycin has recently been studied in biofilm models of *P. aeruginosa*, observing a significant reduction of the biofilm at 24 h compared with monotherapy [14].

The lack of agreement in determining the sensitivity cut-offs between the Clinical and Laboratory Standards Institute (CLSI) (≤64 mg/L) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (≤32 mg/L), the fact that a number of microorganisms require a higher MIC (*Klebsiella* spp., *Enterobacter* spp., *Serratia* spp., *P. aeruginosa*) and the drug's differing effective concentrations against Gram-positive and Gram-negative bacteria have resulted in recommended dosages for treating multidrug-resistant microorganism infections that vary between 8 and 12 g/day for Gram-positive bacteria and 16 and 24 g/day for Gram-negative bacteria [5, 15].

PHARMACOKINETICS/PHARMACODYNAMICS APPROACH

There are 3 fosfomycin formulations: a disodium formulation for intravenous infusion and 2 oral presentations (one calcium and one trometamol). The first formulation consists of 1-8 g of fosfomycin disodium powder with succinic acid as the only excipient. The second formulation is fosfomycin in calcium salt, marketed in a few countries as 500-mg hard gelatin capsules. The third, fosfomycin trometamol, is a derivative of phosphonic acid, available as (1R,2S)-(1,2-epoxypropyl) phosphonic acid with 2-amino-2-(hydroxymethyl)-1,3-propanediol. The formulation is presented in a 3-g packet with white granules of fosfomycin-trometamol.

The pharmacodynamic (PD) ratio of dosage effectiveness for fosfomycin is AUC/MIC. However, the pharmacokinetics PK/PD ratio could be optimized in daily practice based on the pathogen, the patient's clinical profile and the infection model. Fosfomycin exhibits concentration-dependent bactericidal activity against strains of *E. coli*, *P. mirabilis* and *Streptococcus pneumonie* and time-dependent bactericidal activity against *S. aureus* and *P. aeruginosa* [16.17]. By optimizing fosfomycin in Monte Carlo simulations, the PK/PD ratios with which an effective therapeutic objective could be reached (probability of target attainment [PTA] >40%) against enterobacteria are T>MIC over 70% and AUC/MIC >23 [18]. Fosfomycin's molecular stability at room temperature could allow for continuous infusions in complex infection models, alone or combined with other antimicrobials. For example, Asuphon et al. provided the results of the continuous infusion of 16-g fosfomycin combined with an extended infusion of meropenem (1-2 g of infusion for 3 h every 8 h) against clinical isolates of multidrug-resistant *P. aeruginosa*, achieving a cumulative fraction of response (CFR) greater than 88% [19]. A PTA and CFR ≥ 90% are considered optimal against a bacterial population, while a CFR or PTA between 80% and 90% is associated with a moderate chance of success.

Fosfomycin is a fairly safe antimicrobial. Exceptional cases of intolerance have been reported due to the saline overload that fosfomycin can generate. A gram of fosfomycin sodium provides 0.33 g (14.4 meq) of sodium [20], such that a treatment of 12-24 g of fosfomycin provides between 4 and 8 g of salt to the extracellular compartment. Cases of dyspnea and intolerance to decubitus have been reported in patients undergoing treatment with fosfomycin, even with normal ejection fractions, which have required withdrawal of the drug [21-23]. Monitoring the response of the extracellular compartment when faced with saline overload during high-dosage treatments (16-24 g/day) could be useful for patients with comorbidities and water balance disorders (hepatic cirrhosis, heart failure or renal failure) to avoid precipitating an episode of clinical heart failure [24]. The continuous infusions enabled by fosfomycin's molecular stability at room temperature could in turn allow for lower prescribed dosages (12-16 g/day), ensuring plasma concentrations above 32 mg/L, decreasing the total saline overload that would require a fractionated dose. These lower dosages could be especially beneficial for patients with the aforementioned dyscrasias.

A recent review by Falagas et al. [4] examined the kinetics of various formulations of fosfomycin. The oral bioavailability of fosfomycin trometamol ranged from 34% to 58%. Absorption occurs mainly in the small intestine. Although evidence suggests that joint administration with food delays the absorption, renal recovery of the drug does not vary (50-60%) and is not affected by age. The trometamol formulation is absorbed 6-fold more than the calcium formulation during the first 2 h after dosing and approximately 3 to 4-fold more than the calcium formulation during the 12-h period after dosing. The concentrations of a single 2-g dose of fosfomycin trometamol are 2 to 4-fold higher than those of a one 3-g dose of the calcium formulation. The explanation lies in the fact that fosfomycin calcium is hydrolyzed and inactivated by gastric juices [4].

The serum elimination half-life (t1/2) of fosfomycin trometamol is approximately 5 h. A study with healthy volunteers showed serum fosfomycin disodium concentrations of 10 mg/L and 4 mg/L 4 h and 8 h, respectively, after administering a dose of 40 mg/kg. The same fosfomycin doses administered orally (trometamol) presented similar serum concentrations [25]. Further pharmacokinetic studies are needed, given the potential utility of this oral drug in sequential therapy for various infection models, especially in the urinary tract, where the drug concentration is high [4].

APPROACH TO CURRENT CLINICAL PRACTICE

Fosfomycin has been employed for treating urinary and respiratory infections, meningitis, otitis, neurosurgical infections, endocarditis, bacteremia, cardiac surgery, nosocomial infections by extensively drug-resistant *P. aeruginosa* and *Acinetobacter baumannii* and carbapenemase-carrying enterobacteria. Fosfomycin has also been employed for gynecological infections, as well as for device-related and osteoarticular infections by methicillin-resistant and methicillin-susceptible *S. aureus*, among others.

In terms of urinary tract infections, 93-99% of fosfomycin is excreted unaltered in urine and barely binds to plasma proteins, disseminating widely in the renal parenchyma, bladder and uninflamed prostate [6]. Thus, for example, maximum concentrations in urine are reached 2 h after administering a 3-g dose of fosfomycin trometamol orally, with concentrations varying between 1,053 mg/L and 3,749 mg/L, maintaining a mean concentration above 128 mg/L.

A systematic review showed that orally administered fosfomycin trometamol achieved 80% microbiological eradication in cystitis in treated patients, with clinical healing that exceeded 90%, even for those infections caused by ESBL strains [26]. A 3-g dose of fosfomycin-trometamol on days 1, 3 and 5 was active in uncomplicated cystitis, even when caused by ESBL strains, with clinical success of 78-91% [26, 27]. However, for immunosuppressed (transplantation) or catheterized (urethral stent, double J) patients, the eradication rate decreased to 59% [28].

Fosfomycin is recommended for cystitis in immunocompetent patients, according to the guidelines of the Infectious Diseases Society of America [29], even in conditions with ESBL, as are nitrofurantoin and cotrimoxazole [30]. In Spain, fosfomycin is the empiric treatment of choice for acute cystitis, immunocompetent patients and patients with transplants, according to the recommendations of the Spanish Society of Infectious Diseases and Clinical Microbiology [31, 32]. Oral fosfomycin is also employed in asymptomatic bacteriuria and cystitis for pregnant woman [33]. In the pediatric setting, fosfomycin has numerous advantages for use in urinary tract infections: It is easy to dose, it reaches high concentrations in urine, its adverse effects are uncommon, and it does not affect the intestinal flora. Due to its excellent sensitivity pattern against *E. coli* and other enterobacteria, fosfomycin is also considered one of the treatments of choice for afebrile pediatric cystitis, especially in its trometamol form [34].

Fosfomycin has a synergistic effect in combination with other antimicrobials, especially daptomycin and imipenem, against multidrug-resistant Gram-positive strains [35] and has shown greater dissemination than other antibiotics through biofilms [36, 37]. These two characteristics could be useful for treating osteoarticular infections.

There is evidence of the clinical benefit of fosfomycin in combination with daptomycin and imipenem in bacteremia and endocarditis caused by methicillin-resistant *S. aureus* (MRSA) [22, 38]. There is a study underway comparing the activity of fosfomycin in monotherapy versus that of fosfomycin combined with daptomycin in treating MRSA infection [39]. In Spain, the combination of fosfomycin and daptomycin is recommended for treating persistent or complicated MRSA infection in the management guidelines of the Spanish Society of Infectious Diseases and Clinical Microbiology [40]. In the pediatric setting, an alternative could be considered for patients with acute MRSA-induced hematogenous osteomyelitis or for those with beta-lactam allergies [41].

The benefit of combined therapies for multidrug-resistant Gram-negative bacteria has been reinforced by the results of the recent INCREMENT study, which showed that the therapies had less impact on mortality in patients with the most severe conditions (scores >7) with bacteremia caused by carbapenemase-producing enterobacteriaceae [42]. High-dose intravenous fosfomycin and fosfomycin in combination with other antimicrobials have been shown to be useful for treating infections by multidrug-resistant Gram-negative bacteria such as extensively drug-resistant or pan-resistant carbapenemase-carrying enterobacteria and *P. aeruginosa*, especially in urinary tract infections, as well as abdominal, skin and soft tissue infections [43-45]. These formulations are recommended as alternative treatments in combination against urinary tract infections caused by carbapenemase-carrying enterobacteria with an MIC greater than 8 mg/L [46] and for immunosuppressed patients with solid organ transplants [47].

Lastly, the first results of the ZEUS study were presented in March 2019. The study compared fosfomycin against piperacillin-tazobactam for treating complicated urinary tract infections, including pyelonephritis. The randomized study included 465 patients, 233 treated with fosfomycin and 231 treated with piperacillin-tazobactam. In the microbiologically eligible population, fosfomycin fulfilled the primary objective of noninferiority compared with piperacillin-tazobactam, with overall success rates of 64.7% (119/184 patients) and 54.5% (97/178 patients), respectively. The clinical cure rates in the test of cure (TOC) on days 19 to 21 were high and similar between the two treatments (90.8% for fosfomycin [167/184] versus 91.6% for piperacillin-tazobactam [163/178]). In the post-hoc analysis with pathogens typified through pulsed-field gel electrophoresis, the overall success rates in the TOC by modified intent-to-treat were 69.0% (127/184) for fosfomycin versus 57.3% (102/178) for piperacillin-tazobactam (difference of 11.7%; 95% CI 1.3, 22.1) [48].

The new challenges that fosfomycin must address for its implementation in clinical practice include sequential orally administered therapy (once the focus of infection has been controlled and the bacteremia cleared) and optimization of the dosage and galenical oral formulation to achieve these objectives from the pharmacodynamic standpoint (effective concentration in the focus and in blood), with minimal gastrointestinal intolerance. Being able to include fosfomycin in oral sequential therapy for other infection models (beyond urinary) would be enthusiastically welcomed in the stewardship programs.

We are therefore dealing with a compound that, although it has been known for some time, has much left to be discovered. The more we know of this compound, the more potential benefits will be encountered. The most attractive therapeutic model at this time, given its safety and activity, is probably that of urinary tract infection. However, there is increasing in vitro and in vivo evidence of fosfomycin's usefulness in synergistic combination with other antimicrobials for treating complex infections by resistant microorganisms.

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Current key topics in fosfomycin

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New microbiological aspects of fosfomycin

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ABSTRACT

The discovery of fosfomycin more than 40 years ago was an important milestone in antibiotic therapy. The antibiotic's usefulness, alone or in combination, for treating infections caused by multidrug-resistant microorganisms is clearer than ever. Both the European Medicines Agency and the US Food and Drug Administration have open processes for reviewing the accumulated information on the use of fosfomycin and the information from new clinical trials on this compound. The agencies' objectives are to establish common usage criteria for Europe and authorize the sale of fosfomycin in the US, respectively. Fosfomycin's single mechanism of action results in no cross-resistance with other antibiotics. However, various fosfomycin-resistance mechanisms have been described, the most important of which, from the epidemiological standpoint, is enzymatic inactivation, which is essentially associated with a gene carrying a *fosA3*-harboring plasmid. Fosfomycin has been found more frequently in Asia in extended-spectrum beta-lactamase-producing and carbapenemase-producing *Enterobacterales*. Although fosfomycin presents lower intrinsic activity against *Pseudomonas aeruginosa* compared with that presented against *Escherichia coli*, fosfomycin's activity has been demonstrated in biofilms, especially in combination with aminoglycosides. The current positioning of fosfomycin in the therapeutic arsenal for the treatment of infections caused by multidrug-resistant microorganisms requires new efforts to deepen our understanding of this compound, including those related to the laboratory methods employed in the antimicrobial susceptibility testing study.

Keywords: Fosfomycin; Mechanisms of resistance; Susceptibility testing study; Biofilms; Antimicrobial combinations.

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BACKGROUND

Fosfomycin, a bactericidal antibiotic produced by, among others, *Streptomyces fradiae*, was discovered by a Spanish team from the Spanish Penicillin and Antibiotics Company (*Compañía Española de Penicilina y Antibióticos*) in 1969. Since then, fosfomycin has been employed in numerous countries for various indications, both in its intravenous (disodium salt) and oral formulations (calcium salt or trometamol). In recent years, the use of fosfomycin has increased spectacularly due to the considerable incidence of multidrug-resistant microorganisms for which fosfomycin constitutes, alone or in combination, a treatment alternative [1,2]. Due to the considerable usage differences worldwide, the need to establish common criteria and the need to expand the knowledge on this antibiotic, the European Medicines Agency has opened a process that seeks to collect evidence supporting fosfomycin's indications and authorize and harmonize its usage criteria in Europe (https://www.ema.europa.eu/en/medicines/human/referrals/fosfomycin-containing-medicinal-products). Moreover, the US Food and Drug Administration included fosfomycin (according to the laboratory that conducts clinical trials of this antibiotic) in the list of drugs with antimicrobial activity (qualified infectious disease product), which facilitates a priority review of the results of the clinical trials and an accelerated registration process (https://www.nabriva.com/pipeline-research).

The implementation of epidemiological surveillance studies that include fosfomycin, the new clinical trials of this antimicrobial, as well as the pharmacokinetics-pharmacodynamics (PK-PD) studies necessary to support its formulation and to understand the significance of the possible development of resistances have deepened our microbiological understanding of this drug. The aim of this article is to review this new evidence from a microbiological standpoint that supports its clinical use.

MECHANISM OF ACTION AND PHARMACODYNAMICS OF FOSFOMYCIN

Fosfomycin has a single mechanism of action: blocking the first step of peptidoglycan synthesis. The transport of fosfomycin to the interior of the bacteria is performed through permeases, such as the glycerol-3-phosphate transporter (GlpT) and glucose-6-phosphate [G6P] transporter (UhpT). While GlpT maintains baseline activity without being induced, UhpT lacks activity in the absence of G6P. Once inside the bacterial cell, fosfomycin inhibits the UDP-N-acetylglucosamine enolpyruvyl transferase (MurA) enzyme, responsible for catalyzing the formation of N-acetylmuramic acid (precursor of peptidoglycan) through the binding of N-acetylglucosamine and phosphoenolpyruvate. Fosfomycin is an analog of phosphoenolpyruvate, with an epoxide ring (essential in its mechanism of action) and a phosphonic group. Fosfomycin binds covalently with MurA, inhibiting the latter and thereby causing lysis of the bacterial cells (figure 1).

Fosfomycin is therefore a bactericidal compound that acts on bacteria in the growth phase. The fact that Gram-positive and Gram-negative bacteria require the formation of N-acetylmuramic acid for the synthesis of peptidoglycan means that fosfomycin's spectrum of action is very broad. Likewise, there is no possibility of crossed resistances with this compound. Fosfomycin has therefore been employed for treating infections by multidrug-resistant pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant coagulase-negative staphylococci (MRCNS), vancomycin-resistant enterococci (VRE), penicillin-resistant *Streptococcus pneumoniae*, extended-spectrum beta-lactamase (ESBL)-producing *Enterobacterales*, carbapenemase-producing *Enterobacterales* (CPE) and multidrug-resistant *Pseudomonas aeruginosa* [3].

In terms of its physical-chemical properties, fosfomycin is a low-molecular-weight, water-soluble compound with low plasma protein binding that disseminates easily to most tissues and to the interstitial fluid. Studies have shown that fosfomycin penetrates and reaches relevant concentrations in inflamed tissues, aqueous and vitreous humor, bones and lungs [4]. Likewise, fosfomycin actively accesses the interior of polymorphonuclear leukocytes. The compound is excreted almost exclusively in urine in a nonmetabolized form [5].

The PK-PD parameter associated with the compound's bacteriological activity is not clearly defined and appears to depend on the microorganism. Recent studies have established that the PK-PD parameter that best predicts fosfomycin activity in Gram-negative bacilli (*P. aeruginosa*, *Escherichia coli* and *Proteus* spp.) is area under the curve (AUC)/minimum inhibitory concentration (MIC) [6, 7], while in *S. aureus* and enterococcus, fosfomycin has a time-dependent (T>MIC) behavior [8]. A study also demonstrated a high postantibiotic effect, even at subinhibitory concentrations [9].

Various studies have been published that have sought to elucidate the PK-PD parameter that determines fosfomycin activity in *P. aeruginosa*, with a number of conflicting results. A study using a murine model observed that AUC/MIC is the parameter that best fits fosfomycin activity [6], while another study showed that the antibiotic is time-dependent [10]. Bilal et al. determined that the PK-PD parameter that determines the total bactericidal activity of fosfomycin in *P. aeruginosa* is AUC/MIC, while T>MIC is related to resistance suppression [11].

MECHANISMS OF FOSFOMYCIN RESISTANCE

Fosfomycin resistance can be produced by 3 separate mechanisms: 1) transport impairment, 2) impairment of the target of action and 3) enzymatic inactivation (table 1) [5, 12, 13]. The first of these mechanisms is produced by mutants in chromosomal genes of the transporters GlpT and UhpT or in their regulator genes, impeding fosfomycin from reaching its location of action. This mechanism has been essentially described in *E. coli* and *P. aeruginosa* isolates. In *Acinetobacter baumannii*, it has been shown that mutants in the chromosomal gene *abrp* (essential for the bacteria's growth and involved in wall patency) determine the resistance to fosfomycin, tetracyclines and chloramphenicol.

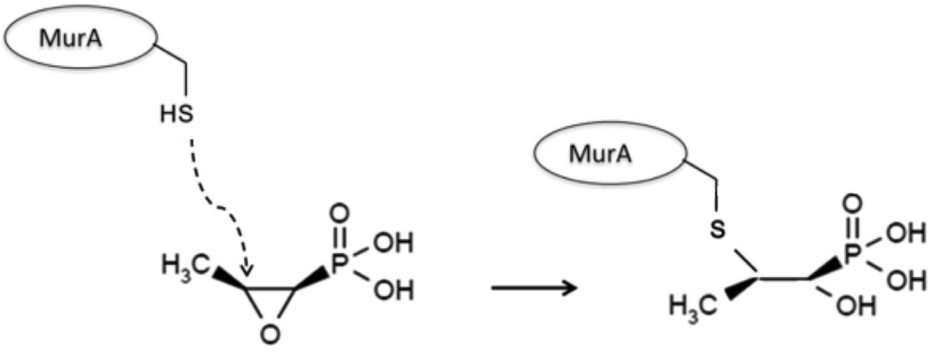

Figure 1 | **Mechanism of action of fosfomycin**

Table 1 Mechanisms of fosfomycin resistance

Process	Resistance mechanism	Microorganism	Localization
Transport reduction	Mutants in transporter genes *glpT* or *uhpT*	*Escherichia coli*	Crom
	Mutants in regulator genes of *glpT* or *uhpT*	*Escherichia coli*	Crom
	Mutants in *cyaA* and *ptsI* (regulate cAMP for *glpT*)	*Escherichia coli*	Crom
	Mutants in *abrp*	*Acinetobater baumannii*	Crom
Change in target or expression	Mutants in *murA*	*Mycobaterium tuberculosis*[a], *Vibrio fischeri*[a], *Escherichia coli*	Crom
	Increased *murA* expression	*Escherichia coli*	Crom
	Alternative pathways to MurA in peptidoglycan synthesis	*Pseudomonas aeruginosa*[b,c], *Pseudomonas putida*[b]	Crom
	Limited participation of MurA in the biological cycle	*Chlamydia trachomatis*[a]	
Inactivation	Inactivation by metalloenzymes by incorporating:		
	-glutathione (FosA, FosA2, FosA3, FosA4, FosA5, FosA6, etc.)	*Enterobacterales*[c], *Pseudomonas* spp[b,c]	Crom / Pl
		Acinetobacter spp.	Crom
	-Bacillithiol or l-cysteine (FosB)	*Staphylococcus* spp., *Enterococcus* spp.	Crom / Pl
		Bacillus subtillis[a]	Crom
	-water (FosX)	*Listeria monocytogenes*[a]	Crom
	Phosphorylation of the phosphonate group by kinases and formation of:		
	-diphosphates and triphosphates (FomA and FomB)	*Streptomyces* spp.	Crom
	-monophosphate (FosC)	*Pseudomonas syringae*	Crom
	(FosC2)	*Escherichia coli*	Pl

[a]Intrinsic resistance; [b]Reduced susceptibility; [c]Some species of *Enterobacterales* (*Serratia marcescens, Klebsiella* spp., *Enterobacter* spp, *Kluyvera georgiana*, etc. have homologous chromosomal *fosA* genes and can present reduced fosfomycin susceptibility); Crom: chromosome; Pl: plasmid

The target of action can be altered intrinsically or by *murA* gene mutants that affect the structure of MurA, with fosfomycin incapable of acting as a substrate. *Mycobacterium tuberculosis* naturally presents MurA with an aspartate residue instead of cysteine in position 117 and is incapable of interacting with fosfomycin, thereby resulting in its intrinsic resistance. Mutants with an altered active center of MurA are found relatively frequently in *E. coli*. The overproduction of MurA also results in insufficient inhibition by fosfomycin, with the microorganism non-susceptible to the action of this antibiotic. In some microorganisms such as *P. aeruginosa* and *Pseudomonas putida*, alternative metabolic pathways independent of MurA have been described in the synthesis of the peptidoglycan that explain the low fosfomycin susceptibility presented by these microorganisms. The lack of susceptibility of *Chlamydia trachomatis* to this antibiotic is due to the lack of importance of MurA in its biological cycle.

However, the mechanism that has attracted the most attention due to its greater epidemiological importance is fosfomycin inactivation, which can be caused by metalloenzymes that efficiently impare this antibiotic, blocking its inhibitory action on MurA. Various metalloenzymes have been described, including FosX and FosA, which inactivate fosfomycin by opening the epoxide ring by incorporating a water and glutathione molecule, respectively. FosB, another metalloenzyme, inactivates fosfomycin by adding a cysteine or bacillithiol molecule, the latter of which is used by Gram-positive microorganisms (Firmicutes) that do not produce glutathione. The incorporation of *fosA* in plasmids and their transformation in *E. coli* raises the MIC values of fosfomycin.

FosX has been found in environmental microorganisms with intrinsic fosfomycin resistance such as *Mesorhizobium loti* and *Desulfitobacterium hafniense* and in pathogens such as *Listeria monocytogenes, Brucella melitensis* and *Clostridium botulinum*. FosA and FosB have an approximate amino acid sequence homology of 48%, and their corresponding genes have been found in the case of *fosB* in plasmids and in the chromosomes of Gram-positive microorganisms (*Staphylococcus epidermidis* and *Bacillus subtilis*) and occasionally associated with plasmids in *Enterobacterales* [14]. The *fosA* gene and its various homologous genes, such as *fosA2, fosA3, fosA4, fosA5* and *fosA6*, have been associated with plasmids in isolates of ESBL-producing *E. coli* and in carbapenemase-producing *Klebsiella pneumoniae*. For *Klebsiella* spp., *Enterobacter* spp., *Serratia marcescens, Kluyvera* spp. and *P. aeruginosa*, *fosA* variants have been identified in their chromosome, with differing sequences but preserving the active center, which could explain the low fosfomycin activity (modal MIC, 4-64 mg/L) in these species when compared with that presented against *E. coli* (modal MIC, 2-4 mg/L) (https://mic.eucast.org/Eucast2/). It has been shown that the deletion of

these chromosomal genes reduces the MIC values of fosfomycin and that its insertion into a plasmid and transformation in *E. coli* confers an increase in MIC values.

Studies have also described kinases (FomA and FomB) that phosphorylate the phosphonate group of fosfomycin, forming diphosphate and triphosphate compounds that lack antimicrobial activity. Another reported kinase is FosC, a homologous phosphotransferase of FomA, which in *Pseudomonas syringae* (another microorganism able to synthesize fosfomycin) converts fosfomycin to fosfomycin monophosphate, which is non-susceptible to MurA.

MICROBIOLOGICAL CONSEQUENCES AND CLINICAL SIGNIFICANCE OF THE DEVELOPMENT OF FOSFOMYCIN RESISTANCE DEVELOPMENT

Despite the considerable ease with which fosfomycin-resistant mutants can be obtained, the clinical repercussion of such mutants has not been sufficiently tested [13]. In some cases, the mechanisms of fosfomycin resistance reduce the fitness of the bacteria that present fosfomycin resistance, and in numerous occasions reduce the bacterial virulence. Such is the case for some mutants in genes that participate in fosfomycin transport, such as *cysA* or *pstI*, which, in *E. coli,* reduce the formation of pili that limit its virulent nature by reducing its ability to adhere to epithelial cells and synthetic materials such as catheters. Lower fitness has also been observed in isolates with MurA overproduction, and its relationship with clinical failure has not been demonstrated. A noteworthy example is that of *L. monocytogenes*, which, *in vitro*, is considered inherently fosfomycin-resistant, not only because it has FosX, which inactivates fosfomycin but also because it is unable of transporting fosfomycin and accessing its location of action. However, *in vivo*, *L. monocytogenes* expresses a permease (Hpt) of G6P, which facilitates the entry of the antibiotic and its susceptibility.

The phenomenon of heteroresistance has been reported in various microorganisms, such as *E. coli*, *A. baumannii, P. aeruginosa* and even *S. pneumoniae*, which indicates the presence of bacterial subpopulations with lower fosfomycin susceptibility. This phenomenon would partly explain the high frequency of mutation for fosfomycin. Resistant mutants can be obtained in up to 40% of *E. coli* isolates at a rate of 10^{-7}-10^{-5}. These mutants present MCIs of 32-64 mg/L, with occasional mutants in genes *glpT* and *uhpT*. Their *in vitro* stability in laboratory media and urine is low, and the typical MIC values can be recovered in successive passages (2-4 mg/L). In approximately 1% of isolates, resistant mutants can be obtained at a lower rate (10^{-11}-10^{-7}) by deletions or insertions in genes *uhpT* and *uhpA*. These mutants present high MICs (512-1,024 mg/L) and lower growth stability than the isogenic strains but greater than that of the *glpT* and *uhpT* mutants [15-17]. These mutants are obtained more frequently in hypermutator strains. However, in all cases, their lower fitness, absence of stability and lower likelihood of selection in acidic environments (e.g., in urine) would also explain the low *in vivo* repercussion of fosfomycin resistance observed *in vitro* [18]. It should be noted that the high concentrations that fosfomycin reaches in some locations, such as urine, and its good penetration in biofilms minimize the possible selection of these mutants. This fact has been demonstrated in *in vitro* models in which the mutant selection window (the concentration range in which resistant mutants would be selected) has been able to be defined. This selection window can be avoided with therapeutic regimens higher than 4 g/8 h [19].

A recent meta-analysis estimated that the risk of selecting resistant mutants during fosfomycin monotherapy in various types of infections (urinary, respiratory, bacteremia, central nervous system and bone) with the involvement of various microorganisms was 3.4% [20]. Resistant mutants were obtained at a higher rate in *Klebsiella* spp., *Proteus* spp., *Enterobacter* spp. and *P. aeruginosa*, the latter of which can reach 20%. This fact could be due to fosfomycin's lower intrinsic activity than that it presents against *E. coli,* which would facilitate its entry into the selection window and justify the administration of fosfomycin in combination with other antimicrobials for infections caused by *P. aeruginosa*. Additionally, a fitness cost associated with fosfomycin resistance in isolates of fosfomycin-resistant *P. aeruginosa* has not been demonstrated, which could reinforce the need for combined therapy in infections caused by this pathogen. These combinations would reduce the selection window in which resistant mutants could be selected [21].

Regardless of the mechanisms detailed earlier, the most important from the epidemiological and clinical standpoint is the enzymatic inactivation associated with *fos* genes. The most important of these genes due to its greater dispersion, plasmid characteristics and presence in ESBL-producing and carbapenemase-producing *Enterobacterales* is *fosA3* [14]. Initially described in 2010, *fosA3* has been found more frequently in Asia, in human and animal isolates, although it is also present in Europe [22, 23]. The rate of *fosA3* varies according to the studied collection but can be present in 90% of fosfomycin-resistant isolates (3-15% of all isolates) that produce ESBL or carbapenemase.

Recently, the origin of the *fosA3* gene in *Kluyvera georgina* has been confirmed. Its integration into plasmids of various incompatibility groups could be related with composite transposons with the insertion sequence IS26 [24].

FOSFOMYCIN SUSCEPTIBILITY TESTING STUDY IN THE LABORATORY, CLINICAL AND EPIDEMIOLOGICAL BREAKPOINTS

The study of *in vitro* fosfomycin susceptibility has always been a challenge in the laboratory due to the lack of unanimous criteria on how it should be conducted for all microorganisms involved in infections for which fosfomycin is indicated. In addition, not all microorganisms currently have interpretive breakpoints (table 2). This situation could change due to the growing interest in this antimicrobial and the need to study it against multidrug-resistant microorganisms in which fosfomycin represents a treatment option.

To date, the reference method recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and the Clinical and Laboratory Standards Institute (CLSI) for the study of fosfomycin susceptibility is agar dilution, adding G6P to the medium (25 mg/L). The justification for this recommendation is that fosfomycin uses 2 types of transporters to penetrate bacterial cells. The first transporter, which has constitutive expression, uses glycerol 3-phosphate. This transporter reduces its activity in culture media that contain glucose or phosphate, which occurs with Mueller-Hinton agar, increasing fosfomycin's MIC values compared with other culture media. The second transporter is induced by the presence of G6P; therefore, when G6P is added to the medium, fosfomycin enters the bacteria more effectively, and its MIC values are drastically reduced. The addition of 25 mg/L of G6P mimics the physiological situation of bacteria at the site of the infection; the MIC values would therefore approach the theoretical values. An increase in the amount of G6P above 25 mg/L in the medium has little effect on the MIC values.

Some microorganisms, such as *P. aeruginosa*, lack a G6P-dependent transporter and only present the glycerol 3-phosphate-dependent transporter. In this case, the addition of G6P to the medium does not change the MIC values [25]. It has recently been shown that fosfomycin activity is increased (lower MIC values) in this microorganism when studied in conditions with limited oxygen availability. This is explained by higher expression of the glycerol-3-phosphate-dependent transporter GlpT, which would resemble that of growth conditions in biofilms and would explain the strong fosfomycin activity against *P. aeruginosa* when grown in these conditions [26].

Although broth microdilution is not recommended for the study of fosfomycin susceptibility testing, a number of authors have demonstrated in *P. aeruginosa* the equivalence of agar dilution and broth microdilution [25]. In *Enterobacterales*, there is a very low correlation between the various methods, including the automatic systems and agar dilution, and are therefore not recommended for the susceptibility study [27, 28].

In the diffusion methods, G6P is added to the disc or to the gradient strips. The disc load recommended by EUCAST and CLSI is 200 µg with 50 µg of G6P. The reading of inhibition zone or ellipses is usually problematic because colonies can appear inside the inhibition zone in up to 41% of *E. coli* isolates. EUCAST has standardized its reading for *E. coli,* proposed that colonies considered susceptible within the inhibition zone should be ignored and has planned to offer recommendations for *K. pneumoniae* and *P. aeruginosa.* Using whole genome sequencing, Lucas et al. [17] recently studied the colonies observed inside the inhibition zone, estimating that only 0.8% of cases were considered resistant when re-examined by disc diffusion. These colonies are mutants whose resistance is due to deletions or nonsense mutants in the *uhpT* gene associated with G6P-dependent fosfomycin transport.

To facilitate reading the inhibition zones or ellipses, reducing the standard inoculum from $1.5x10^8$ to $1.5x10^6$ colony-forming units/mL has been proposed for *P. aeruginosa* [29]. This reduction decreases the presence of inner colonies and improves the correlation with the agar dilution MIC values to better define the wild-type population [MIC less than or equal to the epidemiological cutoff (ECOFF), 128 mg/L]. This approach should also be explored in *Enterobacterales*.

Table 2 **Clinical breakpoints for intrepreting fosfomycin susceptibility testing results**

	EUCAST				CLSI			
	MIC (mg/L)		Inhibition zone (mm)		MIC (mg/L)		Inhibition zone (mm)	
	≤S	>R	≥S	<R	≤S	≥R	≥S	≤R
Enterobacterales	32[a]	32[a]	24[a]	24[a]	64[b]	256[b]	16[b]	12[b]
Pseudomonas spp.	128[c]	128[c]	12[c]	12[c]	-	-	-	-
Enterococcus spp.	-	-	-	-	64[d]	256[d]	16[d]	12[d]
Staphylococcus spp.	32[e]	32[e]	-	-	-	-	-	-
Streptococcus pneumoniae	IE	IE	IE	IE	-	-	-	-
Haemophilus influenzae	IE	IE	IE	IE	-	-	-	-
Moraxella catarrhalis	IE	IE	IE	IE	-	-	-	-

EUCAST, European Antimicrobial Suceptiblity Testing Committee; CLSI, Clinical and Laboratory Standards Institute; IE: insufficient evidence to establish breakpoint values.

[a]Intravenous and oral use (uncomplicated UTI); [b]*E. coli* isolates from the urinary tract; [c]Epidemiological cutoff values (ECOFF) use in combination with other antimicrobials; [d]*E. faecalis* isolates from the urinary tract; [e]Intravenous use

Table 3 **Fosfomycin activity in pathogens with various resistance mechanisms**

Author, date of publication	Microorganism, resistance, (n)	% Fosfomycin susceptibility	Other susceptibility data	Methodology (Breakpoints)	Source of isolate	Country	Ref.
Flamm, R., 2018	*E. coli* (22)/ ESBL *K. pneumoniae* (21)	81.8%/91.7%	MIC_{50}, MIC_{90}= 0.5, 2 mg/L / MIC_{50}, MIC_{90}= 4, 8 mg/L	Agar dilution (CLSI)	SENTRY study	USA	(30)
	E. coli (11)/ Carbapenemase *K. pneumoniae* (12)	92%	MIC_{50}, MIC_{90}= 8, 64 mg/L / MIC_{50}, MIC_{90}= 1, >256 mg/L				
Falagas, M.,2009	MDR/XDR Enterobacterales (152)	98%		Gradient strips (CLSI)	Clinical isolates	Greece	(31)
Bouxom, H., 2018	ESBL *E. coli* and *K. pneumoniae* (100)	92.7%		Agar dilution (EUCAST)	Urinary-bacteremia isolates	France	(35)
Bi, W. 2017	ESBL *E. coli* (356)	92,7%	MIC_{50}, MIC_{90}= 0.5, 32 mg/L	Agar dilution (CLSI)	Urinary isolates	China	(34)
Mezzatesta ML., 2017	ESBL *E. coli* (24)/ KPC *K. pneumoniae* (53)	100%/78%	MIC_{50}, MIC_{90}= 0.5, 1 mg/L / MIC_{50}, MIC_{90}= 32, 128 mg/L	Agar dilution/microdilution/ gradient diffusion (CLSI)	Urinary isolates	Italy	(32)
Flamm, R., 2018	*P. aeruginosa* not susceptible to CAZ-AVI (21)	85.7%	MIC_{50}, MIC_{90}= 32, 128 mg/L	Agar dilution (CLSI)	SENTRY study	USA	(30)
	P. aeruginosa not susceptible to MER (20)	75%	MIC_{50}, MIC_{90}= 32, 128 mg/L				
Walsh C., 2015	MDR and non-MDR *P. aeruginosa* (64)	61%	MIC_{50}, MIC_{90}= 64, 512 mg/L	Agar dilution/microdilution (CLSI)	Cystic fibrosis, bacteremia	Australia	(10)
Perdigao-Neto LV., 2014	MDR *P. aeruginosa* (15)	7%		Agar dilution/microdilution (CLSI)	Urinary, bacteremia and respiratory isolates	Brazil	(38)
Flamm, R., 2018	MRSA (101)	100%	MIC_{50}, MIC_{90}= 4, 8 mg/L	Agar dilution (CLSI)	SENTRY study	USA	(30)
Falagas M., 2010	MRSA (130)	99.2%		Disc diffusion (200) (CLSI)	Nonurinary	Greece	(40)
Lu CL., 2011	MRSA (100)	89%		Agar dilution (NE)	Clinical isolates	Taiwan	(41)
López Díaz MC., 2017	MRSA (55)	43.6%	MIC_{50}, MIC_{90}= 128, 512 mg/L	Agar dilution (NE)	Clinical isolates	Spain	(42)
Wu D., 2018	MRSA (293)	46.8%		Agar dilution (CLSI)	Urinary, bacteremia and respiratory isolates	China	(43)
Guo Y., 2017	VRE (890)	85.1% susceptible 13.4% intermediate		Agar dilution (CLSI)	Rectal swabs	USA	(44)
Tang HJ., 2013	VR *E. faecium* (19) VR *E. faecalis* (21)	30% 44%	MIC_{50}, MIC_{90}=128 mg/L	Agar dilution (CLSI)	Clinical isolates	Taiwan	(45)

CAZ/AVI, ceftazidime/avibactam; CLSI, Clinical and Laboratory Standards Institute; ESBL, extended-spectrum beta-lactamase; EUCAST, European Committee on Antimicrobial Susceptibility Testing; KPC, *Klebsiella pneumoniae* carbapenemase; MER, meropenem; MIC, minimum inhibitory concentration; MDR, multidrug-resistant; MRSA, methicillin-resistant *S. aureus*; NS, not specified; VR, vancomycin-resistant; VRE, vancomycin-resistant enterococcus; XDR, extremely drug-resistant

NEW DATA FROM EPIDEMIOLOGICAL SURVEILLANCE STUDIES

The revaluation of fosfomycin in recent years is due to the scarcity of new antibiotic options and the increased incidence of infections by multidrug-resistant microorganisms. Fosfomycin's unique mechanism of action results in no crossed resistances with other antibiotics. Fosfomycin is therefore situated as one of the few therapeutic options for infections by multidrug-resistant microorganisms. The latest studies that detail fosfomycin activity in pathogens with various mechanisms of resistance are listed in table 3.

***Enterobacterales* with extended-spectrum beta-lactamase and carbapenemases.** According to various *in vitro* susceptibility studies, fosfomycin maintains its activity against ESBL-producing and carbapenemase-producing *Enterobacterales*. It has been reported fosfomycin susceptibility rates of more than 80% against these microorganisms. The authors of a recent article that described fosfomycin activity clinical isolates from the US observed 100% (43/43 isolates) susceptibility to fosfomycin in ESBL-producing *E. coli* and *K. pneumoniae* (MIC_{50}/MIC_{90} of 0.5/2 mg/L and 4/8 mg/L, respectively). In terms of CPE, a susceptibility of 81.8% ($MIC_{50/90}$ of 1/>256 mg/L) was observed for *E. coli* isolates and 91.7% ($MIC_{50/90}$ of 8/64 mg/L) for *K. pneumoniae* [30]. A susceptibility of 94.9% was observed in CPE from Greece [31], while 78%

was observed in *K. pneumoniae* with *Klebsiella pneumoniae* carbapenemase (KPC) from Italy [32].

A review by Falagas et al. [33] that collected *in vitro* data calculated a fosfomycin susceptibility of 96.8% and 81.3% for ESBL-producing *E. coli* and *K. pneumoniae*, respectively. In China, a susceptibility of 92.7% was observed in *E. coli* with ESBL from urinary infections. The resistance in most isolates was associated with a plasmid that carries the bla_{fosA} and bla_{CTX-M} genes [34]

In a study that compared the antibiotic susceptibility of fosfomycin with that of other noncarbapenem antibiotics in *Enterobacterales* with ESBL, 98% of the isolates were fosfomycin-susceptible, while 100% were ceftazidime-avibactam-susceptible, 97% were susceptible to amikacin and piperacillin-tazobactam, and 96% were nitrofurantoin-susceptible [35].

Although these data demonstrated high susceptibility rates in this type of microorganism, an increase in fosfomycin-resistant isolate was reported in Spain during a 4-year period, which was attributed to the increased use of this antibiotic in community-acquired urinary tract infections and to the dispersion of epidemic clones [36]. Likewise, PD studies conducted using time-kill curves and *in vitro* models of emergence of resistant mutants in enterobacteria with ESBL and/or carbapenemases showed not only the bactericidal activity of fosfomycin but also a regrowth of resistant subpopulations that varied according to the species and isolate [37].

Multidrug-resistant *Pseudomonas aeruginosa*. Fosfomycin activity against *P. aeruginosa* is controversial due to the mutation freequency rate at which resistant mutants emerge. There is considerable heterogeneity in the *in vitro* susceptibility results, often due to the method employed for reading the susceptibility. In a study conducted in Australia, 61% of multidrug-resistant and nonmultidrug-resistant *P. aeruginosa* isolates were susceptible to fosfomycin (considering the MIC breakpoint as ≤64 mg/L), with a similar MIC distribution in the 2 groups [10]. In *P. aeruginosa* isolates not susceptible to ceftazidime-avibactam and not susceptible to meropenem, a fosfomycin susceptibility of 85.7% and 75%, respectively, was observed [30]. Much lower susceptibility rates (7%) were observed by Perdigao-Net et al. in Brazil [38].

A review of fosfomycin activity against nonfermenting Gram-negative bacilli collected 19 studies that measured a susceptibility rate in multidrug-resistant *P. aeruginosa* of 30.2%, with a considerable variety of methods employed and different mean susceptibility rates for each of them [39]: microdilution, 91.1% (mean 58.1%, range 0-100%, SD ±45%); agar, 90% (mean 70%, range 0-100%, SD ±41%); disc diffusion, 56.3% (mean 51%, range 0-100%, SD ±35%) and MIC gradient test, 11.1% (mean 28.6%, range 0-93.3%, SD ±35%). Given that agar dilution is the reference method for fosfomycin susceptibility testing, our group has proposed an alternative procedure for implementing the diffusion methods, in which the 0.5 McFarland inoculum is diluted 100 times, which significantly improves the correlation with the reference method [29].

Methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus*. While a number of studies have observed good fosfomycin activity in methicillin-susceptible *S. aureus* (MSSA) and in MRSA, with susceptibility rates of up to 99.2% [30, 40, 41], other studies have reported susceptibility readings of less than 50% in MRSA [42], with differences according to the clonal lineage [43]. Likewise, data on fosfomycin activity against *Enterococcus* vary according to the study. Thus, more than 80% of vancomycin-resistant *Enterococcus faecium* have preserved fosfomycin susceptibility [44] versus 30% reported in other studies [45].

ANTIMICROBIAL ACTIVITY IN BIOFILMS

Fosfomycin has shown a high rate of penetration in mature biofilms of *P. aeruginosa* [46]. Likewise, the anaerobic environment present in the interior of these structures favors the expression of the fosfomycin transporter GlpT. A larger quantity of antibiotic therefore penetrates the interior of the bacteria [26]. There are several *in vitro* and animal model studies that have shown that fosfomycin combined with various antibiotics has the capacity to eradicate or reduce the biofilms of Gram-positive and Gram-negative bacteria. An example of this is the published studies on MRSA biofilms, in which good results have been obtained with fosfomycin combined with vancomycin [47], rifampicin [48], linezolid, minocycline, vancomycin or teicoplanin [49, 50] or with *Enterococcus faecalis* in monotherapy and in combination with gentamicin [8]. Likewise, synergy has been demonstrated against *P. aeruginosa* biofilms in combination with tobramycin, enhancing the penetration of this antibiotic to the cell's interior [51-53].

FOSFOMYCIN ACTIVITY IN COMBINATION WITH OTHER ANTIMICROBIALS

One of the main problems presented by fosfomycin is the high rate at which resistant mutants emerge during the treatment, which, coupled with the lack of crossed resistances and antagonism with other families, means that fosfomycin is administered in most cases in combination with other antimicrobials. There are numerous *in vitro* studies that have sought to elucidate the effect of the combinations, against both Gram-negative bacilli and Gram-positive microorganisms.

Combinations against Gram-negative bacteria. Fosfomycin is one of the few alternatives (along with aminoglycosides and colistin) that present MICs within the susceptibility range in CPE. Therefore, the activity of the combinations of these antibiotics has been studied. The effect of the combination of fosfomycin and amikacin or colistin against KPC-2-producing *K. pneumoniae* was determined in a PK-PD model. A lower resistance rate was observed with the use of the fosfomycin-colistin combination than when colistin was employed in monotherapy [54]. This synergistic effect appears to be due

to the fact that colistin facilitates the entry of fosfomycin into the bacteria's interior, thereby increasing fosfomycin's concentration in the active site. The effect of the fosfomycin-colistin combination appears to depend on the type of strain studied. Thus, the bactericidal effect was not boosted with the combination in colistin-heteroresistant or colistin-resistant strains [55, 56]. *In vitro* synergy with imipenem, ertapenem and tigecycline was also demonstrated in time-kill curves and checkerboard models in KPC-producing *K. pneumoniae* [57].

An interesting combination is the one with phosphonoformic acid (foscarnet) derivatives, an antiviral drug that also possess activity as inhibitor of the FosA enzyme which hydrolyze fosfomycin in Gram-negative microorganisms. Fosfomycin activity is thereby increased in bacteria such as *P. aeruginosa*, *K. pneumoniae* and *Enterobacter cloacae*, which have this enzyme encoded in their chromosome [58] .

The combination of temocillin and fosfomycin has also been shown to be synergistic *in vitro* and *in vivo* and prevents the emergence of resistant mutants when used against *E. coli* with KPC carbapenemases and even OXA-48, which confer resistance to temocillin [59].

In *P. aeruginosa*, there is an alternative pathway bound to the recycling of the peptidoglycan, which prevents its *de novo* synthesis. This fact could explain the lower fosfomycin activity in this microorganism. Peptidoglycan recycling inhibitors have been shown to increase fosfomycin susceptibility [60].

In terms of beta-lactam antibiotics, ceftolozane-tazobactam in combination with fosfomycin has demonstrated *in vitro* synergy, which could be useful for treating infections caused by multidrug-resistant *P. aeruginosa* [61]. Likewise, the combination with meropenem in a model of hollow-fiber infection increased the bactericidal effect and prevented the emergence of resistant mutants [62].

Combinations against Gram-positive bacteria. The combination of fosfomycin and daptomycin is one of the most studied strategies against Gram-positive bacteria. In a recent review that collected cases of infection caused by Gram-positive microorganisms treated with different fosfomycin combinations and the results of time-kill curves in MRSA and MSSA, the combination with daptomycin was shown to be the most effective [63]. An animal model of MRSA endocarditis showed the bactericidal and synergistic action of this combination, where the proportion of sterile vegetations and the bacterial inoculum in the vegetations were also improved [64]. Likewise, daptomycin combined with fosfomycin showed synergy *in vitro* and in a PK-PD model in VRE [65]. In MRSA with intermediate susceptibility to glycopeptides, the combination with imipenem or ceftriaxone was synergistic in an animal model and in time-kill curves [66]. Using time-kill curves and checkerboard assays, *in vitro* synergy has also been demonstrated against MRSA for fosfomycin combined with linezolid [67], rifampicin, tigecycline [68], acid fusidic [69] or quinupristin-dalfopristin [70].

CONCLUSIONS

The microbiological understanding and clinical use of fosfomycin has increased in recent years. However, various aspects still need to be defined, such as those related to its *in vitro* susceptibility study and the PK-PD parameters that best predict its clinical efficacy. Despite this need and the introduction of new antimicrobials with activity against multidrug-resistant microorganisms, the empiric and targeted use of fosfomycin (alone or in combination with other antimicrobials) has increased. It is therefore essential to have fosfomycin in countries with the highest resistance rates, as supported by surveillance studies on resistance and the clinical guidelines.

CONFLICTS OF INTEREST

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Current key topics in fosfomycin

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Deciphering pharmacokinetics and pharmacodynamics of fosfomycin

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ABSTRACT

Fosfomycin, a low molecular weight and hydrophilic drug with negligible protein binding, is eliminated almost exclusively by glomerular filtration, whose clearance is subject to patient renal function. The volume of distribution approximates to the extracellular body water (about 0.3 L/Kg) in healthy volunteers, but it is increased in critically ill patients with bacterial infections. Fosfomycin presents a high ability to distribute into many tissues, including inflamed tissues and abscess fluids. Based on PK/PD analysis and Monte Carlo simulations, we have evaluated different fosfomycin dosing regimen to optimize the treatment of septic patients due to *Enterobacterales* and *Pseudomonas aeruginosa*. As PK/PD targets, we selected $\%T_{>MIC}$ > 70% for all pathogens, and AUC_{24}/MIC > 24 and AUC_{24}/MIC > 15 for net stasis of *Enterobacterales* and *P. aeruginosa*, respectively. Pharmacokinetic parameters in critically ill patients were obtained from the literature. Several dosing regimens were studied in patients with normal renal function: fosfomycin 2-8 g given every 6-12 hours, infused over 30 minutes- 24 hours. At the susceptibility EUCAST breakpoint for *Enterobacterales* and *Staphylococcus* spp. (MIC ≤ 32 mg/L), fosfomycin 4 g/8h or higher infused over 30 minutes achieved a probability of target attainment (PTA) > 90%, based in both $\%T_{>MIC}$ and AUC_{24}/MIC. For MIC of 64 mg/L, fosfomycin 6 g/6h in 30-minute infusion and 8 g/ 8h in 30-minute and 6 hours infusions also achieved PTA values higher than 90%. No fosfomycin monotherapy regimen was able to achieve PK/PD targets related to antimicrobial efficacy for *P. aeruginosa* with MICs of 256-512 mg/L.

Key words: fosfomycin, pharmacokinetic/pharmacodynamic, Monte Carlo simulation, critically ill patients

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PHARMACOKINETICS

Fosfomycin, currently produced by a synthetic method, is a low-molecular weight (138 g/mol), highly polar phosphonic acid derivative (cis-1,2-epoxypropyl phosphonic acid) that represents its own class of antibiotics [1,2]. Fosfomycin was initially marketed as both a calcium salt formulation (fosfomycin calcium) for oral administration and a more hydrophilic salt (fosfomycin disodium) for parenteral administration. Fosfomycin tromethamine, which provides a higher bioavailability (30-40%) [3], was later marketed and has become the standard formulation for oral administration [4].

The pharmacokinetics of fosfomycin, as in general of any antibiotic, is conditioned by pathophysiological changes that occur in the critically ill patient. These changes can impact the concentrations at the site of infection, which may potentially reduce the bactericidal activity [5]. Actually, after intravenous injection, variable peak, mean and trough concentrations have been reported in humans [6]. Table 1 shows the main pharmacokinetic parameters of fosfomycin in critically ill patients [7].

Distribution and tissue penetration. Fosfomycin, a hydrophilic drug with low molecular weight and negligible protein binding (ca. 0%) [8], is highly distributed throughout body tissues, including inflamed tissues and abscess fluids [2]. The volume of distribution (V_d) is consistent with extracellular body water (approximately 0.3 L/Kg) in healthy volunteers [7]. The V_d in critically ill patients with bacterial infections is increased (by as much as 50% in comparison to healthy subjects) probably due to alterations of the vascular endothelium, turning in an increase of capillary permeability [9].

In Intensive Care Unit (ICU) patients with soft tissue infections, fosfomycin has shown to exhibit good penetration into muscle [7], and also into subcutaneous tissues regardless of the presence of inflammation [10]; however, the penetration into abscesses seems to depend on morphological characteristics, such as the permeability of the outer wall or the vascular-

Table 1 **Pharmacokinetic parameter of fosfomycin in septic patients [7].**

Study population	No. of patients	Fosfomycin dose	Pharmacokinetic parameter				
			Vd (L)	t1/2 (h)	Cl (L/h)	C_{max} (mg/L)	AUC_{0-4} (mg h/L)
Sepsis	12	8 g i.v.	31.5±4.5	3.9±0.9	7.2±1.3	357±28	721±66

ity of the surrounding tissues [11]. Fosfomycin administered by intravenous route seems also to exhibit good penetration into infected lung tissue, reaching adequate levels in pleural fluid [12,13]. Severe lung inflammation during bacterial pneumonia seems not impair fosfomycin penetration, which supports its use in severe pulmonary infections [13]. Different studies confirm that fosfomycin presents also a favorable penetration into tissue sites traditionally considered to be associated with low penetration, which supports its potential for use in many difficult-to-treat infection sites [5, 14]. Thus, fosfomycin has the ability to cross the blood-brain barrier, and in case of meningeal inflammation, the concentration in cerebrospinal fluid increases [15]. Fosfomycin is also able to penetrate in both cortical and cancellous bone [16], and in aqueous humor [17].

Clearance. Glomerular filtration is almost the only elimination route of fosfomycin, with total clearance being highly correlated with the glomerular filtration rate, measured as creatinine clearance [8]. Actually, variations in renal function among patients justifies pharmacokinetic variability of fosfomycin in critically ill patients [18]. In spite that fosfomycin is almost entirely eliminated unchanged by the kidney, limited information exists on the clearance of fosfomycin in renally-impaired patients. By intravenous route, dose adjustment is recommended in patients with CrCl < 50 mL/min [19]. A recent study including 2 patients undergoing intermittent hemodialysis and extended dialysis showed that, in spite of the efficient tissue penetration of fosfomycin, the extracorporeal elimination can lead to a dramatic decrease of the fosfomycin serum levels [20]. Another study with 12 anuric ICU patients treated with continuous venovenous haemofiltration (CVVH) and receiving 8 g of fosfomycin every 12 h showed a longer mean half-life than found in ICU patients without renal therapy; additionally, the plasma area under the concentration-time curve (AUC) was higher in patients undergoing CVVH than in critically ill patients without CVVH. After a 12 h haemofiltration process, about 77% of fosfomycin was removed. Fosfomycin concentrations in blood resulted to be enough to eradicate relevant pathogens [21]. In any case, additional pharmacokinetic studies regarding dosing in critically ill patients undergoing different dialysis modalities are needed.

PHARMACODYNAMICS

Fosfomycin exerts bactericidal antimicrobial activity against susceptible pathogens by blocking the early stage of bacterial cell wall synthesis [22]. It has a broad spectrum of *in vitro* activity against a variety Gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), and drug-resistant *Enterobacterales* and *Pseudomonas aeruginosa* varieties, including extended-spectrum-β-lactamase (ESBL)-producing and carbapenem-resistant (CR) organisms [19, 23]. Given that there are few available therapeutic options, fosfomycin seems an attractive alternative for the treatment of serious systemic infections caused by multidrug-resistant (MDR) bacteria.

Mutation frequency studies indicated the presence of an inherently fosfomycin resistant *Escherichia coli* subpopulation (agar MIC = 32-64 mg/L) within the standard starting inoculum of a susceptibility test. Given that the inherently fosfomycin-resistant subpopulation has a frequency of 3.5×10^5 and $>1.2 \times 10^9$ at 5 times and 256 times the baseline fosfomycin MIC, respectively, the administration at high dose should be recommended, especially in monotherapy [24]. A recent meta-analysis showed that resistance emerged during fosfomycin monotherapy at rates ranging from < 3% to 17.9% (pooled estimate 3.4%). The authors confirm the generally noted discrepancy between high rates of *in vitro* emergence of resistance and its evidently low clinical relevance [25].

The EUCAST [26] defines the susceptibility breakpoint as ≤ 32 mg/L for *Enterobacterales* and *Staphylococcus* spp. for intravenous formulation. Fosfomycin has exhibited a prolonged post-antibiotic effect (PAE) *in vitro* against strains of *E. coli* and *Proteus mirabilis*, varying between 3.4-4.7 h, and shorter against isolates of *P. aeruginosa* (0.3-5.5 h) and *S. aureus* (0.5-1.4 h) [27, 28].

PHARMACOKINETIC/PHARMACODYNAMIC ANALYSIS

Pharmacokinetic/pharmacodynamic (PK/PD) analysis in combination with Monte Carlo simulation is a very useful tool to optimize the dosing regimens of antibiotics in order to conserve their therapeutic value. The quantitative relationship between a pharmacokinetic parameter and a microbiological parameter (MIC, minimum inhibitory concentration) is known as a PK/PD index. The three main PK/PD indices associated with the effect of the antibiotics are: $\%T_{>MIC}$, that is the percent of the dosing interval in which the drug concentration remains above the MIC; C_{max}/MIC, which is the peak concentration divided by the MIC; and AUC_{24}/MIC, which is the area under the

concentration-time curve measured over a 24-h period divided by the MIC [29].

There is confusion in the literature about whether fosfomycin displays time- or concentration-dependent bactericidal activity. Roussos et al [28] refer that the type of activity may be organism dependent. Fosfomycin exhibits concentration-dependent killing activity against strains of *E. coli, P. mirabilis* and *Streptococcus pneumonie* and time-dependent bactericidal activity against *S. aureus* and *P. aeruginosa* [27,28].

PK/PD analysis and Monte Carlo simulation allow estimating the probability that a certain PK/PD index reaches the value required for antimicrobial efficacy. In this analysis, two different estimations of the clinical outcome can be done. On the one hand, the probability of target attainment (PTA) is defined as the percentage of simulated patients with an estimated PK/PD index equal to or higher than the value related to the efficacy of the antibiotic against a pathogen with a certain MIC. This cut-off value is known as the parmacodynamic target (PDT). As an example, the PK/PD indexes and the PDTs associated with the efficacy of fosfomycin against *Enterobacterales* are $\%T_{>MIC}$ > 70% [30] and AUC_{24}/MIC > 23 (for net stasis) [31].

On the other hand, the cumulative fraction of response (CFR) is defined as the expected probability of success of a dosing regimen against bacteria in the absence of the specific value of MIC, and thus, the population distribution of MICs of country, sanitary area or health center is used. As an example, for the MIC distribution of non-MDR *P. aeruginosa* reported by Asuphon et al. in Bangkok, Thailand, fosfomycin 16 g continuous infusion combined with prolonged infusion of meropenem (1-2 g infusion over 3 hours every 8 hours) achieved CFR > 88% [30]. PTA and CFR ≥ 90% are considered optimal against a bacterial population, whereas a CFR between 80% and 90% are associated with moderate probabilities of success [29].

Based on PK/PD analysis and Monte Carlo simulations, we have evaluated different fosfomycin dosing regimen to optimize the treatment of septic patients due to *Enterobacterales* and *P. aeruginosa*. As PK/PD targets, we selected $\%T_{>MIC}$ > 70% for all pathogens, and AUC_{24}/MIC > 24 and AUC_{24}/MIC > 15 for net stasis of *Enterobacterales* and *P. aeruginosa*, respectively. These targets were selected based on the study by Lepak et al. [31] who demonstrated, in a neutropenic murine thigh infection model, that maximal animal survival was observed at AUC_{24}/MIC ratio exposures comparable to the stasis targets observed in the same infection model. Pharmacokinetic parameters were obtained from a study carried out Joukhadar et al. in critically ill patients [7]. Several dosing regimens were studied in simulated patients with normal renal function: fosfomycin 2-8 g given every 6-12 hours, infused over 30 minutes- 24 hours. Ten-thousand subject Monte Carlo simulations were conducted for each dosing regimen using Oracle® Crystall Ball Fusion Edition v.11.1.1.1.00 (Oracle USA Inc., Redwood City, CA). A log-normal distribution was assumed for Cl and V_d, according to statistical criteria.

Table 2 shows the PTA values obtained for every dosing regimen. At the susceptibility EUCAST breakpoint for *Enterobacterales* and *Staphylococcus* spp. (MIC ≤ 32 mg/L), fosfomycin 4 g/8h or higher infused over 30 minutes, achieved PTA > 90%, based in both $\%T_{>MIC}$ and AUC_{24}/MIC. For MIC of 64 mg/L, fosfomycin 6 g/6h in 30-minute infusion and 8 g/8h in 30-minute and 6 hours infusions also achieved PTA values higher than 90%. In this regard, it is important to bear in mind that the fosfomycin MIC_{90} usually reaches values of 32 mg/L in ESBL-producing *E. coli*, 64 mg/L in ESBL-producing *K. pneumoniae* and MRSA and 512 mg/L in *P. aeruginosa* [32-34]. No fosfomycin monotherapy regimen was able to achieve PK/PD targets related to antimicrobial efficacy for *P. aeruginosa* with MICs of 256-512 mg/L.

A previous study [7] in which the target site penetration properties of fosfomycin was investigated, revealed that after the administration of 8 g IV to patients with sepsis, the concentration in the interstitium and in plasma remained ≥ 70 mg/L during a 4-hours observation period. Considering that the plasma half-life of fosfomycin is <3.5 h, the target site concentrations will reach < 35 mg/L 8 hours after drug administration. Therefore for a MIC of 32 mg/L, twice-daily dosing might be insufficient, unless that fosfomycin is administered in combination with other antibiotics.

Critically ill patients have been shown higher V_d values and a high level of interpatient variability than seen in non-critically ill patients and high doses may be necessary [18]. Although 24 g/day of fosfomycin achieved the PK/PD targets, it may cause side effects, such as hypokalemia and saline overload. Provided that it has been reported that hypokalemia was more frequent when fosfomycin disodium was administered in 30- or 60-minutes infusions compared with a 4-hours infusion and the high doses of fosfomycin can produce overload of sodium, especially in elderly patients with heart failure or cirrosis or in those who are receiving haemodialysis [35, 36].

In view of these results and in agreement with Parker et al. [5], it seems to be opportune for dosing critically ill patients, to increase the daily dosage over the first 24-48 hours (by using loading doses to counter the increased V_d) and then to continue frequent but lower doses, based on estimates of renal function. Another strategy of dosing can be the use of a loading dose and to continue using not so high doses (12-16 g/day) by continuous perfusion, which as observed in table 2, maintain the steady state concentration (C_{ss}) > 32 mg/L.

The combination of fosfomycin and meropenem is synergistic and prevents the emergence of drug resistance in severe infections caused by ESBL-producing *Enterobacterales* and *P. aeruginosa* strains. Docobo-Pérez et al. [37] examined the utility of fosfomycin alone (4 g/q8h) at the very dense inoculum of 10^{10} CFU/mL against ESBL-producing *E. coli* strain with a fosfomycin MIC of 1 mg/L. Fosfomycin as monotherapy reduced the bacterial concentration by 3 $\log_{10}$ CFU/mL. However, mutants able to grow at 256 mg/L appeared after 48 h of treatment and, 24 h later, the resistant mutants replaced the susceptible population. The combination of fosfomycin (4 g/q8h) and meropenem (1 g/q8h) produced a 10-$\log_{10}$ CFU/mL bacterial reduction and sterilization of the bacterial inoculum

Table 2 **The probability of target attainment (%PTA) of various fosfomycin monotherapy regimens.**

	Probability $\%T_{>MIC}>70\%$							
	infusion 30 minutes						infusion 6 hours	
CMI (mg/L)	2 g/6 h	4 g/12 h	4 g/8 h	4 g/6 h	6 g/6 h	8 g/8 h	4g/8 h	8g/8 h
0.03	100	100	100	100	100	100	100	100
0.06	100	100	100	100	100	100	100	100
0.13	100	100	100	100	100	100	100	100
0.25	100	100	100	100	100	100	100	100
0.50	100	100	100	100	100	100	100	100
1	100	100	100	100	100	100	100	100
2	100	100	100	100	100	100	100	100
4	100	100	100	100	100	100	100	100
8	100	100	100	100	100	100	100	100
16	100	97	100	100	100	100	100	100
32[a]	78	20	98	100	100	100	100	100
64	0	0	11	79	100	98	49	100
128	0	0	0	0	23	11	0	50

	Probability $AUC_{24}/MIC > 24$ (for Enterobacterales)				Probability $AUC_{24}/MIC > 15$ (for P. aeruginosa)			
CMI (mg/L)	4 g/12 h	4 g/8 h	4 g/6 h	6g/6h 8g/8h	4 g/12 h	4 g/8 h	4 g/6 h	6g/6h 8g/8h
0.03	100	100	100	100	100	100	100	100
0.06	100	100	100	100	100	100	100	100
0.13	100	100	100	100	100	100	100	100
0.25	100	100	100	100	100	100	100	100
0.50	100	100	100	100	100	100	100	100
1	100	100	100	100	100	100	100	100
2	100	100	100	100	100	100	100	100
4	100	100	100	100	100	100	100	100
8	100	100	100	100	100	100	100	100
16	100	100	100	100	100	100	100	100
32[a]	98	100	100	100	100	100	100	100
64	4	71	99	100	**81**	100	100	100
128	0	0	4	71	0	24	**82**	100
256	0	0	0	0	0	0	0	24

Continuous infusion	12 g/day	16 g/day
Probability C_{ss} > 32 mg/L	100	100
Probability C_{ss} > 64 mg/L	70	98
Probability C_{ss} > 128 mg/L	0	4

In gray, values ≥90%, in bold, values ≥80 and <90%. [a]Fosfomycin EUCAST breakpoint.

after 48 h of treatment. In addition, the combination completely suppressed all clones resistant to fosfomycin at a dose of 12 g/day when employed as monotherapy.

The use of intravenous fosfomycin as monotherapy for systemic infection caused by *P. aeruginosa* may be problematic because the bacterial killing is virtually eliminated at high inoculum, suggesting that combination with other antibiotics is required for this organism [27]. In *in vitro* studies, the combination of fosfomycin with carbapenems has shown good synergistic effects against *P. aeruginosa* isolates. Asuphon et al. [30] through synergy studies using an E-test strips of fosfomycin in combination with meropenem have reported that MIC_{90} for non-MDR *P. aeruginosa* were 512 mg/L for fosfomycin monotherapy, 128 mg/L for fosfomycin combined with meropenem, 8 mg/L for meropenem monotherapy and 3 mg/L for meropenem combined with fosfomycin. The same authors calculated the PTAs for fosfomycin and meropenem used alone or in combination. For non-MDR *P. aeruginosa*, fosfomycin 16 g continuous infusion combined with meropenem 1-2 g, 3-hour infusion every 8 hours achieve approximately 80% PTA for MIC_{90} 128 mg/L of fosfomycin and 3 mg/L of meropenem. However, the loading dose of fosfomycin needed in a continuous infusion regimen will apply. Considering the carbapenem-resistant *P. aeruginosa* subgroup, MIC_{90} were >1,024 mg/L for fosfomycin monotherapy, 192 mg/L for fosfomycin combined with carbapenems, > 32 mg/L for meropenem monotherapy and 6 mg/L for meropenem combined with fosfomycin. For PTA of > 90% of meropenem in combination with fosfomycin, the dosage should be fosfomycin 8 g every 8 hours infusion over 6 hours in combination wtih meropenem 2 g every 8 hours prolonged infusion at MIC_{90} less than 128 mg/L of fosfomycin and less than 6 mg/L for meropenem. In this regard, Sauermann et al. [11] reported, in an *in vivo* study, that the average concentration at steady state of fosfomycin in the abscess fluid after the administration of 8 g every 8 hours was 184 mg/L. This concentration was higher than the MIC_{90} (128 mg/L) of non-MDR *P. aeruginosa* and carbapenem-resistant *P. aeruginosa* against fosfomycin combined with meropenem [30].

Synergism has been also documented between fosfomycin and glycopeptides, linezolid and daptomycin against MRSA and *Enterococcus* spp. [38, 39].

Until more data are available, fosfomycin should not be used as monotherapy to treat systemic infections with either high MICs or with high bacterial densities [27, 37].

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New evidence on the use of fosfomycin for bacteremia and infectious endocarditis

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ABSTRACT

There is growing concern regarding the increased resistance rates of numerous pathogens and the limited availability of new antibiotics against these pathogens. In this context, fosfomycin is of considerable interest due to its activity against a wide spectrum of these microorganisms. We will review the encouraging data on this issue regarding the use of fosfomycin in treating Gram-negative bacterial infections. We will also cover fosfomycin's role against 2 of the main causal agents of bacteremia and endocarditis worldwide (nosocomial and community-acquired): enterococci, whose growing resistance to glycopeptides and aminoglycosides represents a serious threat, and methicillin-resistant *Staphylococcus aureus*, whose infection, despite efforts, continues to be associated with high morbidity and mortality and a high risk of complications. Thanks also to its considerable synergistic capacity with various antibiotics, fosfomycin is a tool for extending the therapeutic arsenal against these types of infections.

Keywords: Fosfomycin, Bacteremia, Infectious endocarditis, Methicillin-resistant *Staphylococcus aureus*, Gram-negative.

BACKGROUND

There has been a worrying increase in the rates of antibiotic resistance among Gram-positive and Gram-negative pathogens, representing an increase in mortality and hospital stays, thereby impelling the search for alternative treatment strategies. Given the limited availability of new antimicrobials, the reassessment of earlier compounds appears to be an interesting option. Fosfomycin has raised considerable interest, given that, despite being an older antibiotic, it remains active against a wide spectrum of problematic pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA), glycopeptide-resistant enterococci and multidrug-resistant enterobacteria. Fosfomycin's single mechanism of action, along with its broad spectrum and synergistic potential with other antibiotics, makes it a promising candidate for treating patients with complex systemic infections.

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FOSFOMYCIN

Discovered in Spain in 1969 [1], fosfomycin is a bactericidal drug that inhibits cell wall synthesis [2], preventing the formation of the N-acetylmuramic acid of the bacterial wall peptidoglycan. This inhibitory action occurs in one step prior to the action of beta-lactams and glycopeptides. Fosfomycin is a water-soluble agent with a low molecular weight (138 g/mol) and very low protein binding, which provides it with high tissue dissemination. Fosfomycin also penetrates and disseminates adequately in biofilms, not only acting on microorganisms but also changing their structure [3]. Fosfomycin is eliminated almost exclusively through glomerular filtration. The pharmacokinetic-pharmacodynamic effectiveness parameter to consider for achieving the therapeutic objective is the area under the curve/minimum inhibitory concentration; fosfomycin also presents a postantibiotic effect.

Fosfomycin's spectrum is broad and covers most Gram-positive and Gram-negative bacteria, including numerous antibiotic-resistant varieties, such as *Staphylococcus aureus*, including MRSA [4], enterococci, including those resistant to vancomycin [5], *Enterobacteriaceae*, including extended-spectrum beta-lactamase (ESBL) producers [6] and *Pseudomonas aeruginosa* (with varying rates of intrinsic resistance) [7]. Fosfomycin exerts immunomodulatory effects by changing the function of lymphocytes, monocytes and neutrophils, as well as the acute response of inflammatory cytokines *in vitro* and *in vivo*. These effects provide greater bactericidal capacity to neutrophils in the presence of fosfomycin compared with other antimicrobi-

als [8]. Fosfomycin's single mechanism of action makes cross-resistance uncommon and enables synergy with other antimicrobials [9], as demonstrated by numerous studies in the literature that will be discussed later. In general, fosfomycin is considered a safe drug. Nevertheless, there have been reported cases of heart failure secondary to sodium overload after the administration of fosfomycin's intravenous formulation [10].

GRAM-NEGATIVE BACTEREMIA

Most data that support the use of fosfomycin in infections caused by multidrug-resistant Gram-negative microorganisms originate from observational studies that involved a very limited number of patients, in which fosfomycin was generally employed as part of a regimen in combination with other agents. All this, coupled with the lack of an additional comparator group, limit the conclusions that can be extracted from the available data.

Bacteremic infections caused by multidrug-resistant Gram-negative microorganisms have a poor prognosis. The early diagnosis and start of optimal antimicrobial therapy are essential for improving results. A cohort study conducted in a Spanish hospital from 2010 to 2012 that included 40 patients with bacteremia by OXA-48 carbapenemase-producing *Enterobacteriaceae* observed a mortality rate of 65%. The patients were mostly elderly with significant comorbidities (57.5% with underlying malignancy) and had been exposed to antibiotics and invasive procedures during their hospitalization. The most common source of bacteremia was urinary. Amikacin, colistin and fosfomycin were the antibiotics that most often maintained their effectiveness against OXA-48 isolates, but none were uniformly active in isolation. The patients were treated mostly with combinations of antibiotics active against the involved pathogen, employing monotherapy only in highly selected cases (patients with less severe infection and controlled foci). Of the 5 patients who were treated with intravenous fosfomycin (4 underwent combined therapy with colistin, and 1 underwent combined therapy with tigecycline), death due to the infection was reported in 2 [11].

Role of fosfomycin. Preliminary data on the use of fosfomycin in combination with other agents for treating bacteremic infections by multidrug-resistant Gram-negative microorganisms are encouraging. There is an ongoing clinical trial whose main objective is to demonstrate the clinical noninferiority of fosfomycin compared with meropenem in the targeted treatment of bacteremic infections caused by ESBL-producing *Escherichia coli*. The multicenter study included patients with bacteremia secondary to urinary tract infection caused by ESBL-producing *E. coli*. Using a randomized assignment system, the patients were assigned to one of the following treatment arms: intravenous fosfomycin disodium 4 g/6 h or intravenous meropenem 1 g/8 h. The secondary endpoints included hospital mortality, mortality at 30 days, recurrence rate, length of stay, safety and the development of fosfomycin resistance [12].

BACTEREMIA/INFECTIOUS ENDOCARDITIS DUE TO *S. AUREUS*

Staphylococcal bacteremia is a severe entity with high morbidity and mortality and a high risk of complications such as hematogenous dissemination and endocarditis. Staphylococcal bacteremia is one of the main causes of bacteremia worldwide (both nosocomial and community-acquired), with an incidence rate that ranges from 10 to 30 cases per 100,000 person-years. Despite efforts to manage this infection, staphylococcal bacteremia continues to present high mortality, as demonstrated by a recent multinational observational study that analyzed databases from several European institutions. The study showed a mortality rate of 29% at 90 days, although this rate varied with patient age, patient characteristics and focus of infection [13]. In addition to high mortality, these infections are associated with high morbidity and healthcare costs due to prolonged hospitalizations and antibiotic therapies. The factors that influence the prognosis of staphylococcal bacteremia can be divided into 2 categories:

First, we have unmodifiable factors that include those associated with the host (e.g., age, comorbidities), with the pathogen (MRSA) and with the focus of infection, where infectious endocarditis is especially prominent (with its currently mortality rate of 16-25%) and where *S. aureus* has become the leading cause of staphylococcal bacteremia in the developed world [14]. It is also worth noting the global increase in the prevalence of MRSA infections and the associated epidemiological changes, which mainly include an increase in age, the presence of more comorbidities and nosocomial acquisition. Additionally, MRSA infection has been identified as an independent risk factor for mortality, as observed in a large, observational, multicenter Spanish study that included more than 600 episodes of MRSA bacteremia, with a mortality rate >30% regardless of the type of antibiotic therapy administered [15].

Secondly and in terms of modifiable factors, we have those related to the management, early diagnosis, control of foci and appropriate antibiotic therapy. Circumstances, such as the location of the infection, a high bacterial load and the presence of foreign material, as occurs in valve vegetations and abscesses, are especially important because they can hinder management and therapeutic efficacy.

Role of fosfomycin. According to the recommendations of the latest guidelines [16, 17], vancomycin is currently considered the first treatment option for MRSA bacteremia and endocarditis, along with daptomycin (both in monotherapy). However, therapeutic failures have been reported in the literature, as well as the emergence of resistances both to vancomycin and to daptomycin that can reach 15% [18, 19]. Specifically, MRSA strains with MICs for vancomycin ≥2 mg/L have increased from 5.6% in 2004 to 11.1% in 2009 and are associated with poorer results [20, 21].

In this context, fosfomycin can play an important role in broadening the therapeutic arsenal against this type

of infection because it presents very good activity versus methicillin-susceptible *Staphylococcus aureus* (MSSA) and MRSA, with susceptibility rates >95%.

Combined therapy. Several studies have also analyzed the synergistic capacity of fosfomycin with various antibiotics [10]. In the specific case of MRSA, studies have observed that MRSA reduces PBP2A expression in the presence of fosfomycin, thereby increasing the susceptibility to beta-lactams. Experimental models of endocarditis (*in vitro* and *in vivo*) have therefore evaluated the effectiveness of fosfomycin combined with various beta-lactams against MRSA and strains intermediate to glycopeptides. Of these combinations, the one with imipenem is the most active [22]. This multicenter study assessed the clinical efficacy and safety of fosfomycin combined with imipenem as rescue therapy for 16 patients with MRSA endocarditis or complicated bacteremia. The blood cultures became negative 72 h after the first doses in all cases, and the cure rate was 69%, with only 1 death attributable to MRSA. The combination was safe in 94% of the cases, although a patient with hepatic cirrhosis died of multiorgan failure secondary to sodium overload [23]. More recently, the same team conducted a randomized clinical trial to assess the safety and efficacy of imipenem combined with fosfomycin in treating MRSA bacteremia and endocarditis, compared with vancomycin alone. Although the study had defects in its recruitment, and the final sample did not allow for a robust analysis, the study provided a proof-of-concept that warrants future investigations [24].

Although the experience is limited, synergistic *in vitro* activity has been observed between fosfomycin and daptomycin, and some cases have been treated successfully [25, 26]. A clinical trial currently underway [27] randomized patients with MRSA bacteremia to treatment with daptomycin in monotherapy or in combination with fosfomycin. There are also studies on the synergistic activity with linezolid, with good *in vitro* results [28].

In 2013, the guidelines of the Spanish Society of Chemotherapy on the treatment of staphylococcal infection [29] placed fosfomycin as a therapeutic option to consider in MRSA endocarditis on native valves. More recently, other guidelines [18, 30] have included the use of fosfomycin as an alternative in combination with cloxacillin, daptomycin or imipenem for treating infections complicated by MSSA or MRSA.

Bacteremia by *S. aureus*, including infectious endocarditis, entails high mortality, and up to 50% of patients experience failure with the initial therapy with vancomycin and require rescue therapy. New strategies (including the use of fosfomycin) are therefore needed to effectively treat these patients and could require combined therapies such as rescue therapy.

BACTEREMIA/INFECTIOUS ENDOCARDITIS DUE TO *ENTEROCOCCUS* SPP.

Enterococcus spp. has become the third leading cause of nosocomial bacteremia, which is significantly associated with the risk of developing infectious endocarditis [15]. Infectious enterococcal endocarditis is mainly caused by *Enterococcus faecalis* (90% of cases) and, more rarely, by *E. faecium* (5%). The medical treatment of enterococcal endocarditis is a challenge for 2 reasons: 1) Enterococci are highly resistant to antibiotic-induced death, and suppressing enterococci requires extended administration (up to 6 weeks) of synergistic bactericidal combinations of 2 cell-wall inhibitors (ampicillin plus ceftriaxone) or a cell-wall inhibitor with aminoglycosides, and 2) enterococci are resistant to numerous antibiotics such as penicillins and cephalosporins and have a growing resistance to glycopeptides and aminoglycosides [31]. The combination of high-dose penicillin or ampicillin and an aminoglycoside (streptomycin or gentamicin) typically cures enterococcal endocarditis; however, resistance to aminoglycosides is a significant problem and threat. New therapeutic options such as synergistic combinations should be assessed [10]. Fosfomycin could therefore have a useful role, and its combination with ceftriaxone could be considered a therapeutic option in the antibiotic treatment of endocarditis by *E. faecalis* [32].

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The role of fosfomycin in osteoarticular infection

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ABSTRACT

Osteoarticular infections include septic arthritis and osteomyelitis, with Gram-positive microorganisms isolated most frequently. In recent years, there has been an increase in the number of resistant strains in this type of infection, which complicates the treatment. Fosfomycin is active against a large percentage of Gram-positive and Gram-negative pathogens, including multidrug-resistant strains, and its properties include low protein binding, low molecular weight and good bone dissemination. In this article, we discuss fosfomycin's activity *in vitro*, its pharmacokinetic and pharmacodynamic parameters of interest in osteoarticular infections, the experimental models of osteomyelitis and foreign body infection and the clinical experience with these types of infections.

Keywords: fosfomycin, arthritis, osteomyelitis

BACKGROUND

Osteoarticular infections include septic arthritis and osteomyelitis. For septic arthritis, we can differentiate between monoarticular (the knee being the most commonly affected joint) and polyarticular forms, the latter of which usually involves small peripheral joints. Osteomyelitis has been classified according to the degree of impairment of the bone's anatomical structure (medullar, superficial, localized or diffuse) and the pathophysiology of the infection. The latter classification includes the hematogenous infections, which mainly affect the axial skeleton (spine) in adults and long bones in children, which correspond to medullary forms of the anatomical classification. Infections by contiguity include osteomyelitis secondary to bone exposure due to loss of skin integrity (diabetic foot, pressure ulcer) and initially correspond to superficial anatomical forms, although they can progress to localized or diffuse forms if not treated promptly. Lastly, we have osteomyelitis by direct inoculation of the microorganism, which encompasses infections secondary to open fractures and to contamination during the surgical act. The risk of osteomyelitis after an open fracture depends on the severity of the injury; more than 20% of severe cases are still complicated by osteomyelitis. However, the most common form of osteomyelitis at present is the result of bacterial contamination during surgery to place orthopedic material for fractures or for prosthetic joints to treat osteoarthritis. The etiology of osteoarticular infections is dominated by Gram-positive cocci (GPC), although in recent years Gram-negative bacilli (GNB) are on the increase, particularly in infections related to the placement of orthopedic material [1-3].

Prosthetic joint infections (PJI) occur in 1-3% of cases according to data from the Catalonian Nosocomial Infection Surveillance Program (VINCAT), which included more than 7000 annual procedures performed in various hospitals [4]. The aging of the population, with high indices of comorbidity (diabetes mellitus, obesity), and an increase in resistant microorganisms that could potentially contaminate the surgery leads to the prediction that infection rates will not decrease, which will result in significant economic costs [5]. GPC are still the most commonly isolated pathogens, mainly *Staphylococcus aureus* and coagulase-negative staphylococci (CNS). Recent data show that methicillin-resistance rates are approximately 20% and >60%, respectively, for *S. aureus* and CNS; for fluoroquinolones, the resistance rates are >30% in a series in our setting [3, 6]. This fact is important because the best results have been achieved with a combination of levofloxacin and rifampicin, thanks to their increased activity versus bacterial biofilms [7, 8]. An epidemiological study of these infections in 19 Spanish hospitals between 2003 and 2012 showed an increase in GNB and their increased resistance to fluoroquinolones [3],

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a relevant finding because, in these cases, the inclusion of a quinolone in the treatment also improves the prognosis, once again thanks to its increased activity versus biofilms [9,10]. The most worrying fact of the study, however, is that 16% of the infections were caused by a multidrug-resistant Gram-positive or Gram-negative microorganism. This situation warrants an analysis of therapeutic alternatives, which include fosfomycin due to its good activity against multidrug-resistant GPC [11] and GNB [12], its good bone dissemination and activity against *S. aureus*, enterococcus and GNB in various foreign body infection models when fosfomycin is combined with other antibiotics. It is therefore worth reviewing fosfomycin's characteristics in terms of its *in vitro* and *in vivo* activity, as well as the clinical experience in osteoarticular infections with the aim of identifying its indications and forms of administration.

CHARACTERISTICS OF FOSFOMYCIN'S *IN VITRO* ACTIVITY

Fosfomycin is a broad-spectrum, time-dependent bactericidal antibiotic that acts by inhibiting the synthesis of N-acetylmuramic acid and blocking the synthesis of the bacterial wall [13], although its activity is lower in the presence of a high inoculum (10^8 colony-forming units/mL), as can be found in some forms of osteomyelitis [14], suggesting the need for employing fosfomycin in combination. The minimum inhibitory concentration required to inhibit the growth of 90% (MIC_{90}) of staphylococci (regardless of methicillin sensitivity) is <16 mg/L, <8 mg/L against *E. coli* and ≤32-64 mg/L against 50% of strains of *K. pneumoniae*, *Enterobacter*, *Serratia* and *Proteus* and 20% of *P. aeruginosa* strains. One of the peculiarities of fosfomycin's activity is that it maintains an acidic pH [5-7], even in anaerobiosis. There are numerous mechanisms that determine the bacterial resistance within the biofilm, but one of the characteristics of these structures is that the environment in the deeper strata is acidic and oxygen-poor [15]. These data could explain the good results obtained *in vitro* with fosfomycin against biofilms of *S. aureus* and CNS [16, 17]. Although not all of the *in vitro* models demonstrated the efficacy of fosfomycin against biofilms [18], there is greater unanimity in the synergy between fosfomycin and vancomycin, teicoplanin, linezolid and fusidic acid against biofilms of methicillin-resistant *S. aureus* (MRSA). A number of the models showed superior results for fosfomycin compared with those obtained with the combination of these antibiotics and rifampicin [19]. There are also data indicating synergy between ciprofloxacin and fosfomycin (both at concentrations 3 times the MIC) against *P. aeruginosa* biofilms [20]. In the pathogenesis of osteomyelitis, there is increasing evidence of the role of intracellular forms of *S. aureus* that adapt to this location through the formation of small colony variants that present tolerance to multiple antibiotics [21]. Fosfomycin has shown efficacy against intracellular forms of *S. aureus* at therapeutic concentrations, although fosfomycin was unable to prevent the selection of small colony variants, unlike ofloxacin and rifampicin, which suggests the need to employ fosfomycin combinations for this type of infection [22]. These results have been transferred to animal models of osteomyelitis and foreign body infection, with good results as we will discuss later.

PHARMACOKINETIC AND PHARMACODYNAMIC PARAMETERS OF FOSFOMYCIN

There are 3 presentations of fosfomycin: the disodium salt for intravenous administration, the calcium salt and trometamol for oral administration. The oral bioavailability of the calcium salt and trometamol is <20% and <40%, respectively. Therefore, only the intravenous presentation is recommended for treating osteoarticular infections. The intravenous administration of 4-8 g achieves a serum concentration of 200-400 mg/L and an elimination half-life of 3 h. The protein binding is <5%, and the molecular mass is 138 g/mol. The fosfomycin concentration in bone and subcutaneous cell tissue was measured using microdialysis in 9 patients with diabetes and osteomyelitis who were administered a single 100-mg/kg dose. The patients underwent surgery to excise necrotic tissue, leaving the microdialysis needle in the vicinity of the infected bone tissue and subcutaneous cell tissue [23]. The area under the curve (AUC) described by the concentration in the bone and subcutaneous cell tissue was 43% and 76% of the plasma AUC, respectively. The maximum concentration reached in the bone was 96 mg/L, and in all cases the concentration at 6 h remained above 32 mg/L. Considering that the pharmacodynamic parameter that predicts fosfomycin's efficacy is a time above the MIC ≥50%, these data suggest that the dosage of 100 mg/kg (according to the adjusted weight) every 8 h is appropriate for microorganisms with MICs ≤32 mg/L. In the presence of a suppurative collection, especially if it cannot be drained immediately, the recommendation is a loading dose of 10 g to avoid delays in reaching the desired concentration [24]. These data could partly explain the results of experimental models of osteomyelitis that are described in a subsequent section.

Fosfomycin has been classically assumed to easily select resistant mutations, given that it has been determined in the laboratory that the frequency of these mutations in *S. aureus* is relatively high (10^{-6}-10^{-5}), and the mutant prevention concentration (MPC) is 64 mg/L, which, according to the bone dissemination data, suggests that the risk of selecting mutations is high. However, an *in vivo* foreign body model that exposed animals to concentrations between the MIC and MPC (mutagenic window) was unable to select resistant mutations [14]. Similarly, mutations were not selected during treatment of infections caused by *E. coli* [25]. The authors did not identify a loss of competence in the resistant strains, and therefore the reason for this finding should be sought in another characteristic of fosfomycin. It has recently been shown that the bactericidal activity of neutrophils and macrophages is performed not only after phagocytosis in the interior of phagolysosomes through oxidative reactions but also at the extracellular level through the release into the medium of a DNA mesh and molecules with antimicrobial action (elastase, myeloperoxidase) that trap microorganisms and have bactericidal action [26].

Fosfomycin has been shown *in vitro* to potentiate both bactericidal activity pathways of the immune system [27], which could explain the lack of selection *in vivo* of resistant mutations, even when the concentration is within the mutagenic window.

EXPERIENCE WITH FOSFOMYCIN IN EXPERIMENTAL MODELS OF OSTEOMYELITIS AND FOREIGN BODY INFECTION

An experimental model of chronic osteomyelitis by MRSA [28] showed that monotherapy with fosfomycin achieves curing rates >90% and was more effective than daptomycin at a dosage corresponding to 6 mg/kg/24 h. Fosfomycin-resistant mutations were not selected in any case. Foreign-body infection models that seek to simulate infection related to orthopedic implants (osteosynthesis material, prosthetic joints) include the model that introduces a titanium needle into the tibia of a rat that was subsequently contaminated with a high bacterial inoculum. A second model, known as the box model, consists of subcutaneously placing a multiperforated Teflon box containing the inoculated study microorganism into the animal. For the first model, there are 2 studies that assessed the efficacy of fosfomycin, vancomycin, daptomycin and the combination of daptomycin and fosfomycin against MRSA [29, 30]. In monotherapy, fosfomycin was significantly more effective than vancomycin and daptomycin, and the combination with daptomycin was synergistic. Fosfomycin-resistant mutations were not selected in any case, and it is worth noting that all models described herein employed fosfomycin dosages that, in the animal, involved levels lower than those that can be achieved in humans with a dosage of 8 g/8 h.

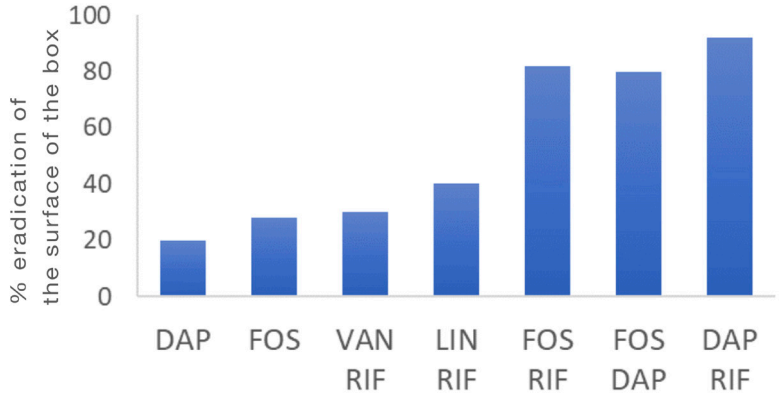

Figure 1 Percentage eradication of an methicillin-resistant *Staphylococcus aureus* biofilm in the animal model of foreign body infection [32-38].

DAP, daptomycin; FOS, fosfomycin; VAN, vancomycin; RIF, rifampicin; LIN, linezolid.

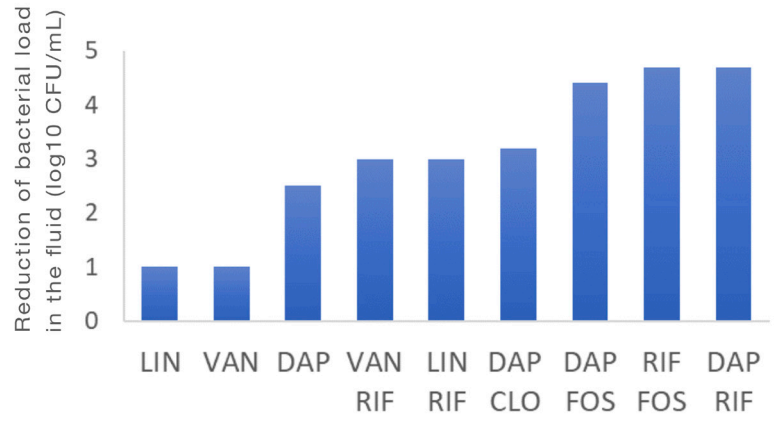

Figure 2 Decrease in bacterial load in the interior of the box of the foreign body animal model by methicillin-resistant *Staphylococcus aureus* [32-38].

CLO, cloxacillin; DAP, daptomycin; FOS, fosfomycin; LIN, linezolid; RIF, rifampicin; VAN, vancomycin.

Table 1 Summary of the clinical experience with fosfomycin in osteoarticular infections

Author/ year	Study type	No. of patients / Infection type	Isolated microorganism, %	Fosfomycin dosage	Combination	Mean intravenous antibiotic duration, days	Mean follow-up, months	Remission n/total evaluated, %
Portier/ 1985 [38]	Prosp.	6 patients: 4 arthritis 2 OM	MRSA (100)	50 mg/kg, 6-8 h	Cefotaxime	15	-	100
Meissner/ 1989 [39]	Prosp.	60 / chronic OM	*S. aureus* (56,7) SCN (25) *P. aeruginosa* (16,7)	5 g / 8 h (loading of 5 or 10 g)	-	13.9	37	73,6
Corti/2003 [40]	Retrosp.	103 children / acute OM	*S. aureus* (60,5)[a] SCN (15,8) *S. pyogenes* (7,9)	-	3 groups: - fosfomycin (23) - fosfomycin + another antibiotic (47) - nonfosfomycin antibiotic (33)	17.5 21.7 26.6	-	23/23 46/47 (98) 32/33 (97)
Luengo/2018 [41]	Retrosp.	1/ chronic hip prosthesis infection	Multidrug-resistant *S. epidermidis*	2 g / 6 h	daptomycin 700 mg / day	42	24	100

CNS, coagulase-negative staphylococci; MRSA, methicillin-resistant *Staphylococcus aureus*; OM, osteomyelitis; Prosp, prospective study; Retrosp, retrospective study.
[a]Calculated for 38 patients with a microbiological isolate.

The box model evaluated 2 factors: 1) the reduction of microorganisms inside the box (planktonic population) and 2) the number of sterilized boxes or the number of microorganisms attached to the box, in the event sterilization was not achieved (sessile population). The efficacy of fosfomycin in monotherapy was limited against MRSA, unlike that observed in models of osteomyelitis; however, the combination with daptomycin and rifampicin was highly synergistic, and both combinations were more effective in reducing the planktonic and sessile populations, with box sterilization rates >70% [31, 32]. Figures 1 and 2 summarize the activity of various antibiotics against MRSA described in several studies conducted with the box model [32-38]. Once again, the selection of a resistant mutation was exceptional.

The box model has been employed to study the efficacy of fosfomycin against *E. faecalis* and extended-spectrum beta-lactamase (ESBL)-producing *E. coli*. Against *E. faecalis*, fosfomycin in monotherapy sterilized 43% of the boxes and increased significantly with the combination of gentamicin to 58% [39]. Against ESBL-producing *E. coli*, fosfomycin in monotherapy was more effective than tigecycline, gentamicin and colistin, but the combinations with fosfomycin improved the results. Specifically, the combination of fosfomycin and colistin achieved sterilization of the box in 67% of the cases [40]. Studies with this model have not been conducted for other microorganisms with few therapeutic alternatives, such as vancomycin-resistant *E. faecium* (VRE), methicillin-resistant CNS, other ESBL/carbapenemase-producing enterobacteria and *P. aeruginosa*, for which *in vitro* data have shown interesting results with fosfomycin in combination with daptomycin against VRE [41] or with carbapenem against *P. aeruginosa* [42, 43].

CLINICAL EXPERIENCE IN TREATING OSTEOARTICULAR INFECTIONS WITH FOSFOMYCIN

The clinical experience with employing fosfomycin in osteoarticular infections is limited to the small case series listed in table 1. In the first series [44], the authors studied the *in vitro* bactericidal activity of several cephalosporins in combination with netilmicin, amikacin, vancomycin and fosfomycin in 10 strains of MRSA. The combination of cefotaxime and fosfomycin was the most active and was assessed in 6 patients with osteoarticular infection (4 with septic arthritis and 2 with osteomyelitis) by MRSA. The treatment consisted of 25-mg/kg cefotaxime administered intravenously and 50 mg/kg/6-8 h of fosfomycin for a mean of 15 days. All patients tolerated the treatment well and presented clinical and microbiological cure with no recurrence, although the authors did not specify the duration of the follow-up after completing the antibiotic regimen. The authors confirmed that the combination was synergistic against the strains isolated from the 6 patients. A second study assessed the addition of 5 g of fosfomycin every 8 h intravenously (with an initial bolus of 5 or 10 g) to antibiotic

therapy for 60 patients with chronic post-traumatic osteomyelitis [45]. The microorganisms isolated most frequently were *S. aureus* (56.7%), CNS (25%) and *P. aeruginosa* (16.7%), all of which were sensitive to fosfomycin. After a mean follow-up of 37 months, 54.7% of the patients had an excellent treatment response, while 26.4% experienced treatment failure. In 19 cases, the fosfomycin concentration could be determined in the bone, and all were higher than the MIC_{90} value of the isolated microorganism. Lastly, Corti et al. [46] assessed 103 children between the ages of 1 month and 15 years with acute hematogenous osteomyelitis, caused mainly by *S. aureus*. The patients who underwent treatment with fosfomycin in monotherapy (n=23) were compared with those treated with fosfomycin in combination with another antibiotic (94% with a beta-lactam) (n=47) and with those who were administered any other regimen without fosfomycin (n=33). The mean intravenous treatment duration was 2.5, 3.1 and 3.8 weeks for the 3 groups, respectively, and only 1 patient in the fosfomycin group required surgical drainage during hospitalization. All patients progressed favorably during the therapy, with C-reactive protein levels normalizing at 2 weeks, except for 1 patient (2%) in the combination group and 1 patient (3%) in the group without fosfomycin who experienced a recurrence.

The clinical experience with the use of fosfomycin in prosthetic joint infections is limited to a single recently reported case of infection by multidrug-resistant *S. epidermidis* treated with debridement, daptomycin (10 mg/kg) and fosfomycin (2 g every 6 h), whose outcome at 2 years of follow-up was favorable [47].

CONCLUSIONS

Fosfomycin maintains good activity against Gram-positive and Gram-negative microorganisms, even for a large percentage of multidrug-resistant strains. Fosfomycin also has good bone dissemination, and an animal model of foreign body infection and numerous *in vitro* studies have demonstrated its activity against biofilms. The antibiotic has noteworthy synergistic activity with daptomycin, rifampicin, vancomycin, linezolid and fusidic acid against biofilms of Gram-positive pathogens, as well synergistic activity with colistin and ciprofloxacin against Gram-negative pathogens. Although clinical experience is limited, fosfomycin employed in combination can be effective in treating osteoarticular infections.

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Current key topics in fosfomycin

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Oral and intravenous fosfomycin in complicated urinary tract infections

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ABSTRACT

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

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

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

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

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

THE MICROBIOLOGY OF COMPLICATED URINARY TRACT INFECTION

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

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

FOSFOMYCIN: MAIN CHARACTERISTICS

Fosfomycin is an antibiotic derived from phosphonic acid, initially isolated in 1969 through cultures of *Streptomyces* spp. [14]. Fosfomycin has a bactericidal action through the inhibition of the UDP-N-acetylglucosamine-3-0-enolpyruvyl transferase (MurA) enzyme in the first steps of peptidoglycan synthesis in the bacterial wall [15]. Fosfomycin also acts by reducing the adherence of bacteria to some epithelia, such as the urinary epithelium [16]. The antibiotic has also shown an immunomodulatory effect by suppressing the production of tubular necrosis factor-β and a number of interleukins (IL-1β, IL-2, IL-8, etc.), as well as improving the phagocytic activity of neutrophils [17]. With regard to its action on biofilms, previous studies on animal models have shown that fosfomycin not only decreases or eradicates biofilms but can also modify their structure *per se*. Fosfomycin has been studied alone and in combination with other antibiotics, such as vancomycin and quinolones, for treating infections caused by *Staphylococcus* spp. [18] and *P. aeruginosa*, respectively [19].

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

FOSFOMYCIN'S SPECTRUM OF ACTIVITY AGAINST UROPATHOGENS

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

Table 1 **Fosfomycin susceptibility in studies since 2010**

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

KPC, *Klebsiella pneumoniae* carbapenemase; MRSA, methicillin-resistant *Staphylococcus aureus*.

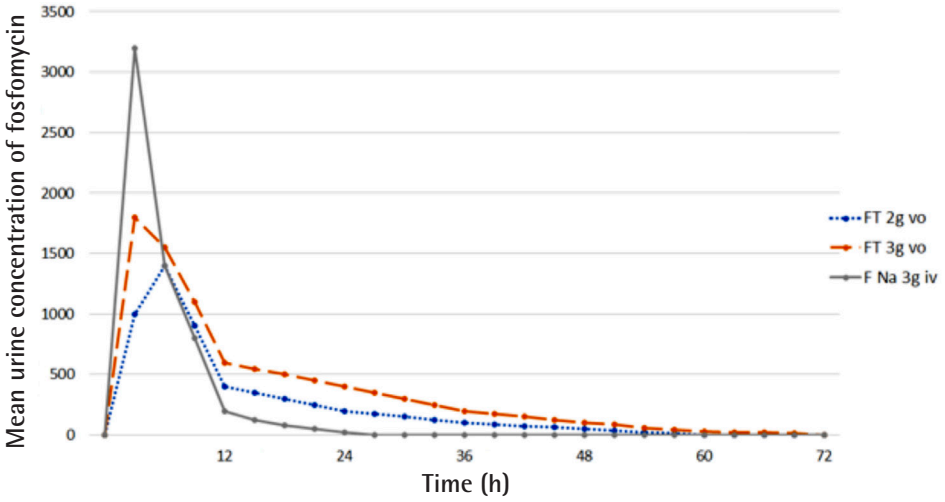

Figure 1 **Mean urine concentration of fosfomycin after 2 and 3g of fosfomycin trometamol (FT) oral (vo) and 3 g of intravenous (iv) fosfomycin disodium (F Na). Adapted from Bergen et al [45].**

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

MECHANISMS OF RESISTANCE

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

PHARMACOKINETICS AND PHARMACODYNAMICS OF FOSFOMYCIN IN URINARY TRACT INFECTION

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

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

FOSFOMYCIN IN ANIMAL MODELS OF URINARY TRACT INFECTION

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

CLINICAL EXPERIENCE WITH FOSFOMYCIN FOR TREATING COMPLICATED URINARY TRACT INFECTIONS

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

Various studies have sought to assess the efficacy of multiple doses of fosfomycin trometamol in cUTI (recurrent and/or caused by multidrug-resistant microorganisms). With regard to prospective studies, Mozdzan et al. assessed the efficacy of fosfomycin trometamol (3 g every 30 days for 12 months) versus nitrofurantoin (administered every 12 h for 7 days and then every night for 12 months) in postmenopausal women with diabetes and recurrent lower UTI, with 50 patients assigned to each group. At 3 months, 89% and 91% of the trometamol and nitrofurantoin groups, respectively, were asymptomatic, 90% and 92% were asymptomatic at 6 months, and 88% and 88% were asymptomatic at 12 months [50]. Lu-Dong Qiao et al. [51] prospectively and multicentrically assessed the efficacy of three 3-g doses of fosfomycin trometamol administered on days 1, 3 and 5 of the study. The patients were clinically and microbiologically evaluated on days 8 and 15. The study included 335 patients, 105 (29%) of whom were men; 67 (20%) patients presented lower cUTI, and 79 (23%) presented recurrent UTI. The ratio of clinical effectiveness was 73%, 63% and 77%, respectively. In terms of microbiological eradication, 77% of the patients with cUTI and 63% of those with recurrent UTI achieved eradication. A third study prospectively assessed the efficacy of three 3-g doses of fosfomycin trometamol versus intravenous carbapenem for 14 days in patients with lower cUTI produced specifically by ESBL *E. coli*. The study included 47 patients (27 treated with fosfomycin and 20 with carbapenems), with similar baseline characteristics. At least 76% of the patients presented more than one complication, the most common of which were the presence of a urinary catheter, prior surgery and malignancy in the urinary tract. Although there were no statistically significant differences between the groups in terms of clinical and microbiological cure assessed between days 7 and 9 from the end of treatment, both rates were lower in the group treated with fosfomycin than in the group treated with carbapenems: 77.7% and 59.3% for the fosfomycin group and 95% and 80% for the carbapenem group, respectively [52] three times. Pullukcu et al. [53] three times also assessed the use of 2 or more doses of fosfomycin trometamol in patients with UTI by ESBL *E. coli*. The authors retrospectively included 52 patients, 36 of whom had cUTI criteria: urinary catheter, KT, urinary tract abnormality (nephrolithiasis or malignancy) and/or recent manipulation at this level. Clinical cure and microbiological eradication was achieved in 94.3% and 78.5% cases, respectively, with no significant differences in terms of cUTI versus uncomplicated UTI ($p>0.05$).

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

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

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

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

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

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

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

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

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

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

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

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Fosfomycin in infections caused by multidrug-resistant Gram-negative pathogens

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ABSTRACT

The alarming increase in antibiotic resistance rates reported for various pathogens has resulted in the use of alternative treatment policies. Given the fairly limited availability of new antimicrobial drugs, the reassessment of older antibiotics is now an interesting option. Fosfomycin, a bactericidal analog of phosphoenolpyruvate that has been previously been employed as an oral treatment for uncomplicated urinary tract infection, has recently raised interest among physicians worldwide. In general, the advanced resistance described in Gram-negative bacteria suggests that fosfomycin can be an appropriate treatment option for patients with highly resistant microbial infections. This review, which refers to key available data, focuses on the possibility of extending the use of fosfomycin beyond urinary tract infections and against multidrug-resistant Gram-negative bacteria.

Keywords: Fosfomycin, Gram-negative bacteria, Multiresistance, Antibiotic treatment.

FOSFOMYCIN'S PLACE IN THE CURRENT PANORAMA OF RESISTANCE IN GRAM-NEGATIVE PATHOGENS

With the increased worldwide prevalence of bacterial resistance, a need has emerged for developing new antibiotics and recovering old substances when sufficient options are not available. Fosfomycin is a derivative of phosphonic acid, initially described and isolated at the end of the 1960s from cultures of *Streptomyces* species. Fosfomycin behaves as a bactericidal antibiotic analog of phosphoenolpyruvate and has a low molecular weight, broad spectrum and putative activity against various bacteria, including many multidrug-resistant Gram-negative microorganisms. Fosfomycin acts by irreversibly inhibiting cell wall synthesis in an early stage, blocking the first step in this synthesis in UDP-GlcNAc enolpyruvyl-transferase. This single mechanism of action means that cross-resistance with other classes of antibiotics is less likely and enables fosfomycin to retain significant *in vitro* activity against numerous Gram-positive and Gram-negative bacteria, including multidrug-resistant strains. Based on this action, interest in fosfomycin has increased among clinicians and microbiologists worldwide for all potential facets of use.

Resistances in Gram-negative bacteria: treatment possibilities. Over the past decade, the resistances of Gram-negative bacteria have become one of the largest threats to public health worldwide. The severity of infections generated by these bacteria, their considerable capacity for transmission and dispersion through the environment, the difficulty in employing empiric treatment (and even appropriately targeted treatment) and the scarcity of new antibiotics against some Gram-negative bacilli (GNB), such as *Acinetobacter baumannii*, *Pseudomonas aeruginosa, Stenotrophomonas maltophilia* and certain enterobacteria with numerous mechanisms of resistance, has raised enormous concern in healthcare systems worldwide [1]. In addition to the attributable complications, morbidity and mortality that multidrug resistance entails, studies have shown the repercussion of this disease burden on quality of life, disability, induction of dependence and, consequently, on the sustainability of the social and healthcare system.

Multidrug resistance is the most important problem in antibiotic resistance due to the difficulty in treating multidrug-resistant microorganisms and the exponential increase in multidrug resistance over the last decade, not to mention AmpC production and the emergence and dissemination of extended-spectrum beta-lactamases (ESBL) and carbapene-

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mases; these ESBL-producing and carbapenemase-producing strains are the main pathogens involved in nosocomial or healthcare-associated infections. A considerable majority of these strains are characterized by the loss of activity against beta-lactam agents, as well as marked resistance to other families of commonly employed antibiotics, such as quinolones and aminoglycosides, due to the accumulation of numerous resistance mechanisms or the transmission of plasmids that transport genes with additional resistance [2-4].

The limited new options against these types of bacterial strains has meant that, over the last decade, antibiotics such as fosfomycin have gained considerable importance as rescue strategies or as combined therapy options for treating infections caused by these multidrug-resistant bacteria [5]. Recovering these old antibiotics for managing complex infections requires, however, an understanding of and an update on their pharmacokinetic and pharmacodynamic characteristics to optimize the antibiotics' efficacy and minimize the significant adverse events occasionally associated with these agents.

Fosfomycin's spectrum of action against Gram-negative bacteria

Fosfomycin presents good activity against Gram-negative bacteria such as *Haemophilus influenzae* and most enterobacteria (figure 1), including *Citrobacter* spp., *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Proteus vulgaris*, *Serratia marcescens* and *Shigella* spp. [6-8], with a minimum inhibitory concentration (MIC) of 0.25-16 mg/L in most isolates. However, a number of these isolates have been observed to reach MIC values of 64 mg/L. Other enterobacteria such as *Klebsiella oxytoca*, *Enterobacter* spp. and *Morganella morganii* have lower susceptibility to this antibiotic, with an MIC of 16-64 mg/L.

Among the nonfermenting GNB, *P. aeruginosa* and *A. baumannii* present moderate susceptibility to fosfomycin, with similar MIC values of 16-64 mg/L [9]. Fosfomycin itself presents activity against strains of *Aeromonas hydrophila*, *Campylobacter jejuni* and *Yersinia enterocolitica*. Against species of the genera *Bordetella*, *Legionella*, *Pasteurella* and *Vibrio*, fosfomycin's activity is moderate [10, 11]. Species such as *Burkholderia cepacia*, *S. maltophilia* and a number of species of the genus *Acinetobacter* are not susceptible to fosfomycin (figure 1) [9].

Fosfomycin has also shown good activity for penetrating the interior of biofilms of Gram-negative bacteria, both in monotherapy and in combined therapy, showing excellent eradication activity [12-14].

Fosfomycin activity against multidrug-resistant Gram-negative bacteria. In recent years, we have witnessed a marked increase in the resistance to drugs commonly employed for managing various infections by Gram-negative bacteria, such as quinolones, beta-lactams and aminoglycosides. In this context of increasing resistances, classical antibiotics including fosfomycin, chloramphenicol, cephamycins, temocillin, polymyxins (colistin), tetracyclines (minocycline) and glycylcyclines (tigecycline) are still some of the few available options.

Numerous studies have demonstrated fosfomycin's good activity *in vitro* against ESBL-producing enterobacteria. The MIC to inhibit 90% (MIC_{90}) of ESBL *E. coli* strains is typically

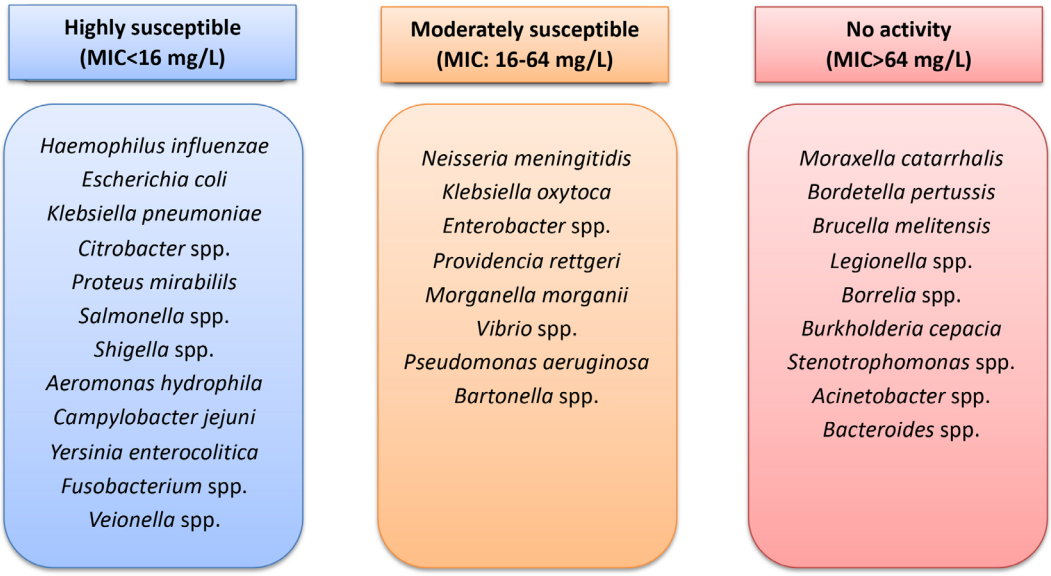

Figure 1 Susceptibility to fosfomycin of Gram-negative bacteria

2-4 mg/L, although Asian countries have observed greater resistance (MIC_{90} of up to 128 mg/L) [15]. Other enterobacteria present a more obvious reduction in their fosfomycin susceptibility after acquiring ESBL. Thus, strains of ESBL-producing *K. pneumoniae* have an MIC_{90} that varies from 32 to >1,024 mg/L [16], greater than that of strains without this resistance mechanism. However, it is worth noting that an increase has been observed in fosfomycin resistance among enterobacteria, with increasing multidrug resistance, in certain geographical regions in recent years. In their study, Rodríguez-Avial et al. showed a significant reduction in fosfomycin susceptibility from 2005 to 2011 in more than 16,000 strains of ESBL-producing *E. coli*. Nevertheless, fosfomycin activity during the last period remained above 80% [17], while ciprofloxacin resistance was 78.2%, cotrimoxazole resistance was 62.3%, and amoxicillin-clavulanate-resistance was 55.3%. In other studies, fosfomycin showed good activity against strains of ESBL-producing *E. coli*, with resistance rates of 2.6% [18] to 10%. Fosfomycin is therefore still a good treatment option in these cases. The impression given by these data and those of other similar studies is that the phenomenon of co-resistance in ESBL-producing enterobacteria related to quinolones and cotrimoxazole is greater and more common and to a much lower degree in combination with fosfomycin.

In terms of carbapenemase-producing enterobacteria (CPE), most of the data come from studies conducted with class A carbapenemase-producing strains of *K. pneumoniae*, known as KPC. The fosfomycin susceptibility of these strains varies between 39% and 100% according to various studies [15, 19, 20]. It is worth noting that fosfomycin also maintains activity against strains of enterobacteria that present the *mcr-1* plasmid, a mobile genetic element known for creating colistin resistance. A study that identified 19 strains carrying this plasmid, among 390 enterobacteria with colistin resistance, showed that they all maintained fosfomycin susceptibility [21].

Fosfomycin activity against nonfermenting GNB such as *P. aeruginosa* and *A. baumannii* in conditions of multidrug resistance is less predictable and varies widely depending on the phenotypes present in the various epidemiological environments [15, 16]. This antibiotic's particular mechanism of action makes it a highly attractive option for use in combination with other agents based on the synergy or addition observed in *in vitro* studies. In fact, there are numerous studies that have demonstrated the clinical efficacy of the combination with antibiotics such as carbapenems and colistin [22-24]. Combined therapy with fosfomycin for managing infections caused by multidrug-resistant Gram-negative bacteria is consistent with the current trends in managing infections caused by these strains [25, 26].

CLINICAL USE OF FOSFOMYCIN IN THE MANAGEMENT OF INFECTIONS BY MULTIDRUG-RESISTANT GRAM-NEGATIVE BACTERIA

Given its pharmacokinetic characteristics (table 1), its particular mechanism of action and its preserved spectrum against multidrug-resistant strains, interest in using fosfomycin has grown significantly and beyond its classical application in managing uncomplicated urinary tract infection.

Infection by multidrug-resistant bacteria. Over the past decade, numerous guidelines and consensuses on managing infections by multidrug-resistant bacteria have been published, which have established alternatives to the use of classical antibiotics. The Spanish guidelines on managing infections by multidrug-resistant enterobacteria include fosfomycin as a relevant option for treating this type of infection, at the same drug level as colistin, tigecycline and aminoglycosides (Level C-III) [27]. Despite limited available experience, the guidelines' authors concluded that fosfomycin could be an appropriate option, at high dosages (4-6 g/6 h or 8 g/8 h) and always in combination with other antibiotics.

A review published by the US Society of Infectious Diseases Pharmacists in 2014 concluded that fosfomycin should be a valid option for managing infections by multidrug-resistant

Table 1 Pharmacokinetic properties and tissue penetration of fosfomycin and other antibiotics employed in managing infections by multidrug-resistant Gram-negative bacteria

	Fosfomycin	Meropenem	Tigecycline	Amikacin
VD, L/kg	0.4-0.5	0.2-0.4	7-9	0.2-0.4
Protein binding	<5%	<5%	75-85%	<5%
Renal clearance	35-50%	75-80%	30%	>95%
Lungs	30-50%	20-40%	5-30%	10-15%
Subcutaneous tissue	40%	70-80%	80-100%	20-30%
Aqueous humor	15%	5-8%	10%	8-10%
Bone	20%	15-20%	350-450%	10%
CSF	65%	5-20%	10-52%	10-20%

CSF, cerebrospinal fluid; VD, volume of distribution; (%) percentage of the property, parameter or degree of tissue penetration.

strains, having shown good tolerance in published studies. The review re-emphasized the need to use fosfomycin in combined therapy due to its synergistic effect with other antibiotics and for minimizing the creation of resistances [28].

Two guidelines on managing infections caused by *P. aeruginosa* have recently been published. The guidelines of the Spanish Society of Chemotherapy (*Sociedad Española de Quimioterapia*, SEQ) consider that fosfomycin could be an option for combined targeted therapy against strains resistant to other antibiotics, in dosages of 16 to 24 g/day [29]. The review published by Bassetti et al. went a step further, indicating that fosfomycin is a possible empiric therapy along with a potentially active beta-lactam for patients with a high suspicion of *P. aeruginosa* infection [30].

Urinary tract infection. Urinary tract infection is the most widely extended indication for fosfomycin, which has been employed since its commercial launch for managing acute and chronic complicated urinary tract infections, both in adults and children. For treating uncomplicated cystitis, the fosfomycin-trometamol formulation constitutes a first-line treatment, along with nitrofurantoin, in 3-g doses in adults and 1-g doses in children [31, 32].

Fosfomycin has gained special importance in recent years in managing complicated urinary tract infections caused by multidrug-resistant strains of Gram-negative bacteria, both intravenously and intramuscularly, at dosages of 12-18 g/day. The use of fosfomycin has been successfully applied in monotherapy and combined therapy with other agents, including aminoglycosides, tigecycline, colistin, piperacillin/tazobactam and carbapenems [33, 34], and shows high response rates against enterobacteria and *Pseudomonas* spp. In fact, a number of authors recommend the use of fosfomycin in sepsis of urinary origin caused by ESBL-producing enterobacteria in which the use of carbapenems is not indicated [32]. Nevertheless, the clinical practice guidelines have still not included the use of fosfomycin among the options for empirically managing urinary sepsis with a high suspicion of ESBL [35-38]. Results are still pending from the FOREST study [39], an interesting clinical trial that is comparing the use of fosfomycin in monotherapy versus meropenem for managing bacteremia of urinary origin caused by enterobacteria. The results will more clearly position fosfomycin in the management of urinary tract infections caused by multidrug-resistant Gram-negative bacteria.

Pulmonary infection. Fosfomycin has shown good penetration (32-53%) in the lung tissue (table 1) of patients with pneumonia compared with the administered dose and the blood concentration reached [40]. Fosfomycin has therefore been proposed as an option for managing pneumonia, predominantly nosocomial, with resistances to the commonly employed antibiotics. It is worth noting that in the published cases of pulmonary infection by multidrug-resistant Gram-negative bacteria successfully treated with intravenous fosfomycin, this antibiotic has been administered in combination with other antibiotics, including carbapenems, tigecycline and colistin [41]. There is also experience in the use of intravenous fosfomycin in combination with other drugs for managing exacerbations caused by *P. aeruginosa* in patients with cystic fibrosis, observing good responses and tolerance to treatment [42]. Fosfomycin is not currently included in the guidelines as empiric treatment for managing nosocomial pneumonia [43], although the limited published experiences might make fosfomycin a consideration in centers with high rates of pneumonia by Gram-negative bacteria and high resistances to beta-lactam when good susceptibility to this antibiotic is maintained.

In terms of adjuvant nebulized therapy, there are several active studies to determine its efficacy in managing pneumonia, primarily in conjunction with aminoglycosides. In a recently published, randomized clinical trial on pneumonia by Gram-negative bacteria associated with mechanical ventilation, the joint administration of fosfomycin and amikacin through a special inhalation system showed no benefits in terms of clinical curing and mortality, compared with the placebo arm and intravenous antibiotic treatment, despite a reduction in bacterial load [44]. Therefore and given the limited and conflicting experience with this pathway, the use of this combination should be reserved for conditions in which there is a suspicion of high pulmonary inoculum and there are no other available options.

Osteoarticular infection. Although Gram-positive microorganisms represent the largest number of cases of osteoarticular infection, infections by Gram-negative microorganisms have experienced a marked increase over the last decade [45], representing an added difficulty for antibiotherapy due to the microorganisms' faculty for developing resistances during extended treatment and the difficulties in selecting active antibiotics with good penetration in osteoarticular tissue (table 1). Sirot et al. [46] measured fosfomycin's capacity for penetrating bone tissue in 20 patients and found that the concentrations reached 1 and 3 h after administering 4-g doses were 19.6 and 10 mg/mL, respectively, representing 15% of the concentrations reached in blood. Other authors have also measured high fosfomycin concentrations in bone and interstitial fluid [47], revealing the treatment option with this drug. In addition, we have fosfomycin's activity against bacteria that form and live in biofilms, which constitute the main mechanism of bacterial persistence in prosthetic joints and the cause of failure in antimicrobial therapy.

In vitro studies have demonstrated fosfomycin's superior eradication activity to other antibiotics such as gentamicin, tigecycline and colistin against strains of ESBL-producing *E. coli* in prosthetic materials [48]. Fosfomy-

cin could therefore be considered a good option in managing infections associated with osteoarticular prosthetics caused by multidrug-resistant strains, although more clinical evidence is needed to recommend its use.

Endocarditis. As with other drugs, information regarding the use of fosfomycin in endocarditis caused by Gram-negative microorganisms is limited, with its activity demonstrated only in animal models [49]. The guidelines of the European Society of Cardiology [50] and Infectious Diseases Society of America [51] therefore do not include this drug as a candidate for managing these types of bacteremic infections of endovascular origin. Nevertheless, this drug has recognized activity against Gram-positive microorganisms such as methicillin-resistant *S. aureus*, where its synergistic activity with antibiotics such as imipenem has been confirmed [52]. This fact means that this combination could be a basis for managing endocarditis by Gram-negative bacteria.

Central nervous system infections. Despite the limited published experience with fosfomycin in managing central nervous system (CNS) infections, 2 of the antibiotic's characteristics make it an attractive option for managing nosocomial CNS infections, in which GNB predominates. Firstly and as mentioned earlier, fosfomycin presents good eradication activity against biofilms, which play a relevant role in persistent infections in patients with ventricular drainage. In a recent study with 1,642 samples of cerebrospinal fluid (CSF) obtained through ventricular drainage, approximately 7.5% showed a positive result for Gram-negative bacilli isolates, with half of the study strains producing biofilms [53]. Fosfomycin exhibits a good capacity for passing through the blood-brain barrier, with approximately 30% penetration [54], which is higher than that of glycopeptides, aminoglycosides and many beta-lactams. Thus, fosfomycin has good diffusion in CSF and CSF collections, both with inflamed and non-inflamed meninges; fosfomycin's C_{CSF} is therefore greater than the MIC of the susceptible bacteria (table 1).

Despite the limited reported experience, there are case series of CNS infections by ESBL-producing enterobacteria successfully treated with fosfomycin [55]. Fosfomycin could therefore be considered an option for managing these infections when there are few therapeutic alternatives.

Gastrointestinal infections. Fosfomycin presents good activity against the main Gram-negative pathogens involved in gastroenterocolitis, including isolates of *Campylobacter, E. coli, Salmonella* spp. and *Shigella* [56]. Moreover, fosfomycin's structure facilitates good diffusion in the gastrointestinal tissue after its systemic administration; fosfomycin has therefore been widely employed for decades for treating these infections [48]. A study of 118 children showed that fosfomycin was able to effectively eradicate strains of Shiga toxin-producing *E. coli* O157:H7 and, consequently, enterohemorrhagic conditions; therefore, the use of fosfomycin in the first 5 days of the disease could reduce the risk and onset of hemolytic uremic syndrome [57]. This protective nature of fosfomycin assumes even greater value when we consider the current controversy regarding the undefined role of antibiotic treatment in this infection and that the previous use of antibiotics could be a significant risk factor for developing the aforementioned syndrome.

In terms of its application for managing secondary or tertiary intraabdominal infection, fosfomycin's activity against ESBL-producing and carbapenemase-producing enterobacteria makes this drug an attractive option, despite the limited experience described to date [58, 59].

FOSFOMYCIN AND STRATEGIES FOR COMBINED THERAPY

In a recent survey conducted within a European study of expert opinions to explore the contemporary antibiotic management of hospital infections caused by carbapenem-resistant, Gram-negative bacteria, the combination of a polymyxin and a carbapenem was the most widely used combination in most cases, although combinations of polymyxin and tigecycline, an aminoglycoside, fosfomycin and rifampicin were also common [60]. Combination therapy was prescribed at least occasionally in 99.1% of the participating hospitals (114 of 115) and was considered more frequently when treating bacteremia, pneumonia and CNS infections, in a similar manner among enterobacteria, *P. aeruginosa* and *A. baumannii*. Monotherapy was employed for treating complicated urinary tract infections, typically with an aminoglycoside or a polymyxin and less frequently with fosfomycin. The aim of combined therapy is to improve treatment effectiveness and prevent the development of resistance. In general, those surveyed shared the erroneous idea that combined therapy (the preferred strategy) was supported by solid, high-quality scientific evidence [60].

In treating intra-abdominal, skin and soft tissue infections caused by carbapenemase-producing enterobacteria, the double combinations of tigecycline and a carbapenem or an aminoglycoside were the most common; for complicated urinary tract infections, the combination of an aminoglycoside and fosfomycin was the most common (34/105, 32.4%). For infections caused by *P. aeruginosa* with carbapenem resistance, the combined treatment bound a carbapenem (54.7% in the case of bacteremia), an aminoglycoside or fosfomycin to the polymyxin (colistin). In triple combination therapy, the polymyxin is bound to a carbapenem and typically more to fosfomycin than to an aminoglycoside to avoid resulting in renal toxicity [60].

The benefit of combined therapies for multidrug-resistant Gram-negative bacteria has been reinforced by the results of the recent retrospective INCREMENT cohort study, which investigated the effect of more appropriate therapy and more appropriate combined therapy on the mortality of patients with bacteremia caused by carbapenemase-producing enterobacteria [61]. Appropriate therapy was associated with a protective effect on mortality, and combined therapy was related to improved survival but only in the patient subgroup classified with a high mortality score at baseline. The authors therefore concluded that to manage bacteremia by carbapenemase-producing enterobacteria, patients should undergo early appropriate therapy as soon after the diagnosis as possible and that monotherapy should be reserved for episodes classified as low mortality using the scale [61]. The most commonly employed combinations were those of colistin plus tigecycline (31%), aminoglycosides plus tigecycline (35%) and colistin plus carbapenem (44%). The overall mortality of the monotherapies was 41% and that of the combined therapies as a whole was 35%, with 33% for the combinations that included fosfomycin, although this antibiotic was used in only 10 of the 343 episodes of bacteremia with appropriate treatment (78% of the series; 22% underwent inadequate treatment). The mortality in the cases of combined therapy with fosfomycin was higher (40%) among the patients with high-risk scores (8-15) than among the patients with low mortality risk scores (0-7). It should be noted that, in this study, the most common microorganism was *K. pneumoniae* (85% of the cases of bacteremia) and that the most common type of carbapenemase was KPC (in approximately 75%).

A recent comprehensive review of treatment for infections caused by AmpC-producing, ESBL-producing and carbapenemase-producing enterobacteria included highly detailed assessments and positioning statements on the role of fosfomycin for managing these infections [62]. Once again, treatment in monotherapy was a possible option in only one series of infectious syndromes, such as urinary tract infections; however, the authors also warned that until the results of a series of studies currently underway are made available [39, 63], firm recommendations cannot be made regarding the treatment of ESBL-producing or AmpC-producing enterobacteria with fosfomycin alone.

For carbapenemase-producing enterobacteria, combined therapies are recommended, given that the efficacy in monotherapy is questionable for a number of the drugs active *in vitro*, including polymyxins, tigecycline and fosfomycin. Thus, the importance of exploring combined therapies to find a potential synergistic or additive effect between some of these antibiotics. Due to the lack of relevant information, fosfomycin is not a first option against severe infections by carbapenemase-producing enterobacteria when there are other active drugs available (even less so in monotherapy) but might be necessary in some patients with few options. Among the explicit recommendations, fosfomycin is included among the accompanying drugs to be added to double or triple combinations, both in combinations where a beta-lactam is the main antibiotic and in those that involve colistin, depending on whether susceptibility is maintained to various beta-lactam agents of potential use (ceftazidime-avibactam or meropenem-vaborbactam; alternatively, meropenem [if the MIC is ≤8 mg/L], ceftazidime or aztreonam). In the case of resistance to beta-lactam and colistin, fosfomycin would accompany an aminoglycoside and tigecycline [62]. In such cases, the recommendation is high dosages of fosfomycin (16 to 24 g per day) in combination.

The usage possibilities for fosfomycin in combined regimens has also been contemplated and included in other recent guidelines on managing infections by multidrug-resistant GNB in recipients of solid organ transplants [64]. In particular, fosfomycin is preferred for use in triple combination therapies, combined with 2 other active antibiotics (a carbapenem only when the MIC is ≤8 mg/L, administered at high dosages and in extended infusions) and especially in urinary tract infections, although it can be used in other infectious syndromes and bacteremia of diverse origin [65]. Only in cases of less invasive or less severe infection, especially urinary, patients could benefit from a carbapenem-free treatment with colistin, aminoglycosides or fosfomycin in monotherapy.

CONCLUSIONS

In an environment of increasing resistance among Gram-negative bacteria, fosfomycin has been positioned as an option to consider in treating infection by these bacteria, due to fosfomycin's sustained activity against these strains and its pharmacokinetic properties and activity against biofilms [66]. The risk of emerging resistant subpopulations under monotherapy should always be considered and thereby prevented. Although susceptibility rates vary by region, the resistances seem to increase in settings with a high use of fosfomycin and along with exposure when faced with multidrug-resistant pathogens [67]. Beyond the urinary infections as the main focus of prescription [68, 69], fosfomycin's excellent capacity for diffusion to various tissues grants it considerable versatility for managing infections by Gram-negative microorganisms in various other types of infectious syndromes [70]. All of this makes fosfomycin one of the key wildcards of combined therapy according to the various guidelines and recommendation documents.

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Current key topics in fosfomycin

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Fosfomycin in the pediatric setting: Evidence and potential indications

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ABSTRACT

To date, there has been little experience in using fosfomycin in children. However, its broad spectrum of action and excellent safety profile have renewed interest in this antibiotic, especially for treating infections by multidrug-resistant bacteria. The main indication for fosfomycin in pediatrics is currently community-acquired lower urinary tract infection. Given its good activity against bacteria, fosfomycin can also be useful in urinary infections caused by extended-spectrum beta-lactamase-producing enterobacteria. Fosfomycin presents very good dissemination to tissues including bone and is therefore an option in the combined therapy of osteomyelitis, especially in cases produced by methicillin-resistant *Staphylococcus aureus* (MRSA) or in cases with beta-lactam allergies. Fosfomycin can also be employed in combination for multidrug-resistant Gram-negative bacteremia (especially carbapenemase-producing enterobacteria), *S. aureus* (if there is a high suspicion of MRSA or complicated infections) and vancomycin-resistant *Enterococcus* spp. Other infections in which fosfomycin could be part of a combined therapy include staphylococcal endocarditis (in case of beta-lactam allergy or MRSA), central nervous system infections (mainly by MRSA, *S. epidermidis*, *Listeria* and resistant pneumococcus), nosocomial pneumonia and infections associated with mechanical ventilation.

Keywords: Fosfomycin, Pediatrics, Children, Newborns, Beta-lactam resistance.

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BACKGROUND

Fosfomycin is a broad-spectrum bactericidal antibiotic, with activity against Gram-positive and Gram-negative microorganisms, including multidrug-resistant bacteria. Fosfomycin presents excellent dissemination to tissues (skin, soft tissue, muscle, bone, lungs, central nervous system) and has shown efficacy in experimental biofilm models [1]. Its unique mechanism of action leads to a synergistic effect with many antimicrobials and makes cross-resistance exceptional [1, 2]. Fosfomycin also presents an excellent safety profile in children [3], even in prolonged therapies [4]. These characteristics make the antibiotic a highly attractive option, especially for treating infections by multidrug-resistant bacteria, although the experience with children is still very limited.

DOSAGE OF FOSFOMYCIN FOR PEDIATRIC PATIENTS

The available formulations and pediatric doses for fosfomycin are shown in table 1 [5, 6]. The recommendations for its parenteral administration are based on highly limited data, especially regarding newborns. Although the datasheet indicates the possibility of intravenous administration every 12 h, pharmacokinetic studies conducted on children show that intervals of every 6-8 h are preferable, except for preterm newborns [7]. In premature infants, the recommendation is 100 mg/kg/day divided into 2 doses; for full-term newborns, 200 mg/kg/day in 3 doses is recommended. Starting at 12 years of age or 40 kg of weight, the dosage is the same as for adults [8]. In the case of infections by multidrug-resistant microorganisms, there are no specific recommendations for children, while for adults the recommendation is 8-12 g/day for Gram-positive microorganisms and 16-24 g/day for Gram-negative microorganisms [9].

For adults, the recommendation is to adjust the dosages for those with kidney failure and creatinine clearance lower

Table 1	Dosage of fosfomycin for pediatric patients
ORALLY	Calcium salt (suspension 250 mg/5 mL, 500-mg capsules)
	Younger than 1 year: 150-300 mg every 8 h
	Older than 1 year: 250-500 mg every 8 h
	Trometamol salt (granules for oral solution, 2 g or 3 g)
	6-11 years: 2 g single dose[a]
	≥12 years: 3 g single dose[a]
PARENTERALLY	Intramuscularly (starting at 2 and a half years): 500-1000 mg every 8 h[b]
	Intravenously: 200-400 mg/kg/day in 3 doses (maximum 4 g/dose[c])

[a]For recurrent infections or microorganisms susceptible to higher dosages, 2 doses might be necessary, with a 24-h interval.
[b]If a larger dose is needed, the intravenous route should be employed.
[c]For children older than 12 years (>40 kg), a dosage of up to 8 g every 8 h may be considered for treating severe Gram-negative infections with reduced susceptibility.

than 40 mL/min; for children, however, there are insufficient data to make dosage recommendations for those with nephropathy [8].

URINARY TRACT INFECTION

Urinary tract infection (UTI) is one of the most common childhood bacterial infections [10]. It is estimated that 7-8% of girls and 2% of boys will have at least one UTI before the age of 8 years. Febrile UTI mainly affects infants (of both sexes), while cystitis mainly occurs in girls older than 3 years [11, 12]. Acute pyelonephritis is especially severe in small infants, who have a greater risk of bacteremia and sepsis [13].

Escherichia coli is the main etiological agent in all age groups [14]. Since the introduction of conjugated vaccines against *Streptococcus pneumoniae*, *E. coli* has represented the most common cause of bacteremia in infants, and more than 90% occurr in children with UTI [15]. In Spain, various epidemiological studies have been conducted in recent years in the pediatric population, in which *E. coli* is the causal agent for 60-80% of UTIs, in patients from primary care, the emergency department and hospitals. Other Gram-negative microorganisms include *Klebsiella*, *Proteus*, *Enterobacter* and *Citrobacter*. Among the Gram-positive bacteria, we have *Enterococcus* (especially in small infants and children with previous nephro-urological conditions), *Staphylococcus saprophyticus* (adolescents) and, in rare cases, *Staphylococcus aureus* [16-18].

The enterobacteria's resistance profile varies due to numerous factors, such as the patient's characteristics and their geographical origin. We therefore need to determine the local resistance rates to make appropriate recommendations on empiric treatment for these microorganisms [19]. In Spain, the most recent studies on the pediatric population have shown that up to 50-60% of *E. coli* are ampicillin-resistant and that 20-30% are cotrimoxazole-resistant; these antibiotics should therefore not be employed in empiric therapy [16-18]. Resistances to amoxicillin-clavulanate appear to be increasing, although with significant local variations [16-18]; it is therefore advisable to employ this antibiotic with caution, especially in those areas where susceptibility is below 85-90%. In contrast, the resistance rates remain below 10% for aminoglycosides, fosfomycin and second and third-generation cephalosporins [16-18].

Treatment with fosfomycin has numerous advantages for use in children with UTI: 1) It is easy to dose, 2) it achieves high concentrations in urine, 3) adverse effects are uncommon, and 4) fosfomycin does not affect the intestinal flora. Due to the excellent susceptibility pattern of *E. coli* and other enterobacteria, fosfomycin is considered one of the treatments of choice for afebrile UTI, especially in its trometamol form [16]. In the case of febrile UTI, fosfomycin is not recommended for use in monotherapy at this time due to the potential development of resistances during therapy [20]. Although the rate at which resistant mutations appear *in vitro* is high, the rate is very low in clinical studies and especially in the case of UTI by *E. coli*, due to the high antibiotic concentration and acidic pH in the urinary tract. The development of resistances could entail a biologic cost for bacteria, with a lower growth rate and adherence to urinary epithelial cells. To establish the role of fosfomycin in severe UTI, data from the FOREST and ZEUS studies, recently conducted on adult patients, will be of considerable assistance. The FOREST study was conducted in Spain from 2014 to 2017 and compared the efficacy of fosfomycin versus meropenem in treating bacteremic UTI by extended-spectrum beta-lactamase (ESBL)-producing *E. coli* [21]. The ZEUS study began in the US in 2017 and compared the safety and efficacy of fosfomycin versus piperacillin-tazobactam in complicated UTI [22].

Although these conditions are still uncommon in children, an increase in infections by ESBL-producing *E. coli* has been

observed in recent years in patients in the community, many times in combination with other mechanisms of antibiotic resistance [19]. It is currently estimated that, in Spain, these bacteria appear in 1-4% of pediatric UTIs [16-18, 23] and are increasingly associated with recurrent UTI [23]. These patients could benefit from fosfomycin therapy [24], given that very high susceptibility to fosfomycin has been demonstrated in ESBL-producing enterobacteria in UTIs [25]. However, there are barely any available pediatric data on this issue [26].

In Spain, *Enterococcus faecalis* presents high susceptibility to fosfomycin [16-18], which would therefore make this antibiotic an excellent option for treating lower UTIs due to this microorganism.

OSTEOARTICULAR INFECTION

Osteoarticular infection is more common in children than in adults, with 50% of cases occurring in children younger than 5 years, with *S. aureus* the most common microorganism in all ages. In newborns and infants younger than 3 months, other significant pathogens are *Streptococcus agalactiae* and enterobacteria; in those younger than 2 years, *Kingella kingae* is a significant pathogen. The fundamental importance of these infections lies in the potential involvement of cartilage and epiphysis, which can alter bone growth and lead to sequelae [27]. In Spain, more than 90% of infections in children are caused by methicillin-susceptible *S. aureus* (MSSA) [27]. In recent years, however, the emergence of community-acquired MRSA has been observed in various countries around the world [28, 29]. Community-acquired MRSA is typically susceptible to other non-beta-lactam antibiotics, and there are various options for their use in pediatrics: clindamycin, cotrimoxazole, glycopeptides, rifampicin, linezolid and daptomycin [30]. In terms of the fosfomycin susceptibility of *S. aureus*, 9 studies have been published between 2010 and 2015, with 7 of the studies showing sensitivities greater than 90%, with similar data in MSSA and MRSA [31]. Fosfomycin also presents excellent penetration in tissues including bone [32].

In France, one of the most widely used empiric treatment regimens in pediatric osteomyelitis is the combination of third-generation cephalosporin and fosfomycin [33, 34]. The results of treating acute hematogenous osteomyelitis with fosfomycin are highly favorable, and fosfomycin could therefore be considered an option for combined therapy, especially in cases produced by MRSA and for patients with allergies [35].

BACTEREMIA AND SEPSIS

Infants. Neonatal sepsis is still a significant cause of morbidity and mortality. Based on the time of onset, the condition is divided into early and late sepsis. Early sepsis typically occurs in the first 72 h of life and is caused by vertical transmission, before or during childbirth. The most common microorganisms involved are *S. agalactiae* and *E. coli*. Late infections occur starting from the third day of life, in most cases by horizontal transmission. In addition to the previously mentioned microorganisms, coagulase-negative staphylococci (the most common cause of sepsis in neonatal intensive care patients), *S. aureus* and Gram-negative bacilli are involved, among others [36]. Prematurity and low birth weight are the main risk factors for neonatal sepsis. Preterm newborns present immune system dysfunction and usually require extended hospitalization, venous accesses and mechanical ventilation, which contribute to a greater risk of infection [36]. Exposure to multiple antibiotic cycles during their hospitalization increases the risk of colonization and infection by multidrug-resistant bacteria [37]. Coagulase-negative staphylococci are still the most common bacteria in late nosocomial sepsis in premature newborns and have high resistance rates. In recent years, however, resistant Gram-negative bacteria have emerged, especially ESBL-producing enterobacteria [37, 38]. These infections present greater severity and are associated with higher morbidity and mortality than those caused by coagulase-negative staphylococci.

Various studies have confirmed the relationship between pathogens isolated in colonization detection programs and subsequent isolates in blood cultures, especially in children with colonization by *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Enterobacter cloacae* and *Serratia marcescens* [39]. Selecting an inadequate empiric antibiotic therapy for a patient with colonization by multidrug-resistant Gram-negative bacteria can result in longer hospitalizations, higher mortality and poorer neurological outcomes [39]. Due to the limited therapeutic arsenal in these cases, a number of authors have proposed assessing the use of fosfomycin in combined therapy [40]. There are currently few data on the pharmacokinetics in newborns, and studies with premature infants are needed to assess the effect of kidney maturation in the clearance of the drug, which could change the administration interval. Specific studies on the drug's toxicity in infants have not been conducted either, although no adverse effects have been reported in patients treated for neonatal sepsis. Future studies should assess the risk of hypernatremia, given the sodium intake that the administration of fosfomycin entails [40].

To date, 2 series have been published on the use of fosfomycin in neonatal sepsis by Gram-negative microorganisms: one with 11 newborns (from a total of 24 patients) with sepsis by *S. marcescens*, most of whom were treated with fosfomycin and gentamicin [4], and another series of 21 patients with combined therapy with aminoglycoside in neonatal sepsis and UTI [41]. In both studies, 90% of the patients had favorable outcomes.

Infants and children. Pediatric sepsis is associated with a significant consumption of healthcare resources. The incidence of pediatric sepsis is higher in infants and children with underlying diseases, especially with immune, hematologic and oncologic diseases [42]. The overall mortality is 6%, increasing to 23% in cases produced by multidrug-resistant Gram-negative microorganisms [43, 44]. The most common causes of bacter-

emia in hospitalized children are coagulase-negative staphylococci, Gram-negative bacilli and *S. aureus* [45].

There are very few data on bacteremia by multidrug-resistant Gram-negative bacilli in the pediatric population. A recent study conducted in Italy within the Antibiotic Resistance and Prescribing in European Children (ARPEC) project analyzed more than 1000 episodes of bacteremia, 26% of which were caused by Gram-negative microorganisms, 39% of which were multidrug-resistant [44]. In these infections, there was synergy in the combination of fosfomycin and carbapenems or colistin [1]; therefore, the use of fosfomycin was proposed within a combined therapy and is the first choice in the case of carbapenemase-producing enterobacteria [46].

There are no pediatric guidelines on treating bacteremia by *S. aureus*. However, the guidelines of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) recommend combined therapy with fosfomycin and daptomycin as a possible option for suspected bacteremia by *S. aureus* with a high probability of MRSA and/or patient instability, secondary bacteremia or complicated infection [47].

In recent years, there has been an increase in nosocomial bacteremia by *Enterococcus* spp., especially in intensive care units (neonatal and pediatric) and hemato-oncological patients [48]. In severe infections by vancomycin-resistant strains, the use of fosfomycin in combination with daptomycin or linezolid may be considered [49].

ENDOCARDITIS

Endocarditis is uncommon in children and mainly affects infants, older children and adolescents with heart disease. The most commonly involved bacteria are streptococci of the *viridans* group in children with heart disease and *S. aureus* in children with no prior heart disease [50]. The mortality of endocarditis in children is 5-10% [51]. The guidelines of the European Society of Cardiology recommend similar treatment regimens for adults and children and list the indication for fosfomycin (in combination with daptomycin) as a treatment option for staphylococcal endocarditis on native valves in patients with allergies to beta-lactams or MRSA infection [52]. The SEIMC guidelines recommend the combination of daptomycin and fosfomycin as the empiric treatment of choice for all cases of endocarditis (native and prosthetic valve) in patients with beta-lactam allergies and as the definitive treatment in native valve endocarditis in cases of beta-lactam allergy or MRSA [47]; the use of this combination could therefore be assessed for children in the same situations.

CENTRAL NERVOUS SYSTEM INFECTIONS

Due to its low molecular weight and low protein binding, fosfomycin's cerebrospinal fluid penetration is high [53] and could therefore also be employed in central nervous system infections. The use of fosfomycin has been reported in infections by MRSA and *S. epidermidis*, typically within combined therapy [54]. In terms of pneumococcus, monotherapy with fosfomycin has failed in experimental meningitis models [55], while combined therapy can be useful in strains with high cephalosporin resistance [56]. In pediatrics, the use of fosfomycin in combination with third-generation cephalosporins has been reported in 2 patients with meningitis by pneumococcus with intermediate cephalosporin susceptibility [57]. The case of an infant with multiple brain abscesses by *Citrobacter koseri* was recently published, which was resolved with surgical drainage and combined therapy with meropenem and fosfomycin [58]. *Listeria monocytogenes* is resistant *in vitro* but susceptible *in vivo* to fosfomycin; the use of fosfomycin in combination with beta-lactams could therefore be assessed for complicated meningoencephalitis by these bacteria [59].

OTHER INFECTIONS

The use of fosfomycin in respiratory infections is poorly documented, despite its good lung dissemination. Currently, the use of fosfomycin in community-acquired pneumonia is not justified given the high susceptibility of pneumococcus to penicillin and cefotaxime [60]. Fosfomycin could be useful within combined therapy in nosocomial pneumonia and infections associated with mechanical ventilation. Fosfomycin has also been employed by inhalation in cystic fibrosis, in combination with tobramycin [61].

In acute gastroenteritis, especially in premature infants, fosfomycin has also been employed with good tolerance [62, 63]. Currently, the antibiotic therapy for these infections is reserved for selected cases (small infants, immunosuppression, severe symptoms), and a number of authors have also proposed antibiotic therapy for conditions in which the transmission of the infection needs to be prevented, such as hospitalized patients and in closed institutions [64]. Given the good fosfomycin susceptibility pattern of the main bacteria that cause gastroenteritis, fosfomycin could also be assessed for use in this indication.

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Fosfomycin in antimicrobial stewardship programs

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ABSTRACT

Due to the increase in antimicrobial resistance, strategies such as antimicrobial stewardship programs (ASP) have been developed to improve the clinical results, decrease the adverse effects and the development of resistances and ensure cost-effective therapies. Fosfomycin has a unique mechanism of action against Gram-positive and Gram-negative bacteria. Cross-resistance is uncommon; however, fosfomycin should be used in combination in severe infections to avoid selecting resistant mutations. Fosfomycin's oral formulation facilitates sequential treatment, has low toxicity and high tissue penetration, even in the central nervous system and bone. Fosfomycin is active against resistant Gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci and penicillin-resistant *Streptococcus pneumoniae*, as well as against resistant Gram-negative bacteria such as extended-spectrum beta-lactamase-producing and carbapenemase-producing enterobacteria. Fosfomycin is therefore useful for cases of persistent bacteremia, skin and soft tissue infections, as a glycopeptide-sparing and carbapenem-sparing drug for healthcare-associated infections and for polymicrobial infections. Published studies have demonstrated the synergy between fosfomycin and beta-lactams, daptomycin and glycopeptides against MSSA and MRSA; with linezolid in biofilm-associated infections and with aminoglycosides and colistin against Gram-negative bacteria, providing a nephroprotective effect.

Keywords: Fosfomycin, ASP, Multidrug resistant microorganisms, Antibiotic synergy.

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The increase in infections caused by multidrug-resistant (MDR) microorganisms is currently one of our greater medical challenges. In fact, antimicrobial resistance is considered by the World Health Organization as one of the greater threats to worldwide health. The problem is aggravated by the lack of a parallel increase in new antibiotics, mainly of agents that offer relevant advantages in treating MDR bacteria [1]. While new compounds are being developed (a long and costly process), a number of "old" antibiotics developed decades ago and whose use was discontinued for various reasons are being repurposed for new indications [2]. This situation has prompted the design and implementation of various strategies to alleviate the problem. One of these strategies is the implementation of antimicrobial stewardship programs (ASP), whose objectives are to improve clinical results, reduce adverse effects related to the use of antibiotics (including resistance) and ensure a cost-effective therapy [3].

One of the lines of action in ASP is the selection of antibiotics that do not promote the emergence of MDR microorganisms. Cephalosporins, quinolones and carbapenems have been associated with the selection of extended-spectrum beta-lactamase (ESBL)-producing enterobacteria, *Clostridium difficile* and MDR *Pseudomonas* [3]. In addition, alternatives need to be found to treat these increasingly resistant microorganisms.

Fosfomycin has a unique mechanism of action against Gram-positive and Gram-negative bacteria, through peptidoglycan synthesis inhibition. This unique mechanism of action implies that cross-resistance is very rare [4]. However, fosfomycin in monotherapy selects resistant mutations and therefore needs to be employed in combination with other agents to treat severe infections. Fosfomycin offers the advantage of its low toxicity and ease of oral administration in sequential treatment (e.g., urinary tract infection), unlike other options such as colistin and tigecycline. Just as other old antibiotics, however, fosfomycin was not subject to a development program as strict as the current programs for authorization; thus,

the necessary pharmaceutical information for developing optimal dosage regimens (maximizing the efficacy and minimizing the toxicity) is limited [5]. Given fosfomycin's potential, studies need to be conducted to determine its efficacy in new contexts and to define its optimal pharmacokinetics/pharmacodynamics index [6, 7].

FOSFOMYCIN IN ANTIMICROBIAL STEWARDSHIP PROGRAMS FOR INFECTIONS BY GRAM-POSITIVE MICROORGANISMS

Fosfomycin can be useful for treating infections caused by drug-resistant Gram-positive bacteria because of fosfomycin's activity against methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant enterococci and penicillin-resistant *Streptococcus pneumoniae* [8, 9]. Due to this spectrum of action, fosfomycin is useful for cases of persistent bacteremia, such as initial or sequential therapy of skin and soft tissue infections, as a glycopeptide-sparing drug for healthcare-related infections and for polymicrobial infections by enterococci, Gram-negative microorganisms and MRSA. Fosfomycin is also a treatment option for nosocomial infections caused by vancomycin-resistant enterococci such as bacteremia, pneumonia or intra-abdominal infections [6].

Its use in combination with other antibiotics reduces the risk of developing fosfomycin resistance during therapy. Several synergy studies have shown that fosfomycin can decrease the penicillin resistance level in pneumococci and methicillin resistance in staphylococci, altering the expression of penicillin-binding proteins. Studies have also been published that demonstrated the synergy *in vitro* between fosfomycin and beta-lactams against methicillin-susceptible *S. aureus* (MSSA) [10]. This combination can therefore be an option in cases of persistent bacteremia [11, 12], although randomized studies are needed to demonstrate the effect of this combination for treating bacteremia by MSSA. A number of experimental studies have demonstrated the synergy between fosfomycin and various antibiotics against MRSA strains. In experimental models of endocarditis (*in vitro* and *in vivo)* that have evaluated the synergy of fosfomycin combined with various beta-lactams against MRSA and strains of *S. aureus* with intermediate glycopeptide susceptibility, the combination of fosfomycin and imipenem was the most active. A multicenter study assessed the clinical efficacy and safety of treatment with fosfomycin and imipenem as salvage therapy for 16 patients with endocarditis or complicated bacteremia by MRSA. The blood cultures became negative within the first 72 h after the first dose, and the cure rate was 69%, with only 1 death attributable to the infection; the combination was shown to be safe in 94% of the patients [13]. Currently, there is an ongoing randomized clinical trial by the same team comparing vancomycin versus the combination of imipenem and fosfomycin in infectious endocarditis by MRSA with the minimum inhibitory concentration (MIC) of vancomycin <2 mg/L [14]. The results could demonstrate that this combination is effective and safe in patients with complicated bacteremia by MRSA and can be a therapeutic option that spares treatments with glycopeptides whose use has been associated with a poor response to new drugs (such as daptomycin).

The synergy between fosfomycin and daptomycin has been studied *in vitro*, and although the experience is limited, there are several reports of cases of bacteremia by MRSA successfully treated with this combination [15, 16]. To assess the safety and efficacy of this combination, an open, multicenter randomized study is underway in Spain comparing this combination versus daptomycin in monotherapy in patients with bacteremia by MRSA [17]. These combinations could therefore be considered in cases of persistent bacteremia or those with a higher risk of complication (e.g., advanced age, significant comorbidity, bacteremia of unknown focus) [18]. For severe infections caused by methicillin-resistant *S. epidermidis*, especially those with a large inoculum (such as endocarditis), the use of antibiotics in monotherapy, including vancomycin at suboptimal dosages, can promote the selection of resistant mutations. The recommendation is therefore to use combinations. The use of vancomycin plus fosfomycin is the best option [19].

The oral formulation of fosfomycin is an added value in treating community-acquired infections, such as skin and soft tissue infections by MRSA. Fosfomycin is also useful for improving sequential therapy in patients infected by resistant bacteria that would otherwise require maintaining intravenous administration, should other options be used. The reduction in hospital stay can be quite significant in some cases. The high concentrations in urine reached by fosfomycin allow for its use in monotherapy against infections by vancomycin-resistant enterococcus in this location [9]. Fosfomycin is a low-molecular-weight molecule with low protein binding, which favors its penetration into the interstitial fluid of subcutaneous cell tissue in healthy patients, patients with diabetes and critically ill patients. Due to its structural similarity to hydroxyapatite, fosfomycin penetrates the bone in adequate concentrations for treating MRSA and other pathogens. Fosfomycin is therefore an alternative for treating diabetic foot infections and osteomyelitis [20], even as salvage therapy in cases of clinical failure or the development of resistances [21]. The use of fosfomycin in combination has an immunomodulatory and nephroprotective effect when employed with nephrotoxic drugs such as aminoglycosides and vancomycin. Based on studies on animal models, this effect is apparently due to the inhibition of histamine release that occurs after the destruction of mast cells [7, 22]. There are even published cases of extended therapy with the combination of vancomycin, aminoglycoside and fosfomycin with no renal function impairment [23].

High dosages of antibiotics and extended durations are necessary for the treatment of infections associated with biofilms. The combination of linezolid and fosfomycin has shown synergy, which could help decrease the dosage of both drugs and reduce the risk of adverse effects such as the thrombopenia and peripheral neuropathy associated with linezolid [24].

FOSFOMYCIN IN ANTIMICROBIAL STEWARDSHIP PROGRAMS FOR INFECTIONS BY GRAM-NEGATIVE MICROORGANISMS

The main objectives of ASP for infections caused by Gram-negative microorganisms is to prevent the emergence of further resistance and to provide a more effective and efficient use of the available antibiotics. The lack of effective antibiotics in the face of increased resistance is especially important in infections caused by Gram-negative microorganisms.

The increase in infections by MDR microorganisms requires the use of very broad-spectrum empiric antibiotics such as carbapenems, often with no options for de-escalation. A number of old antibiotics repurposed in new indications have significant toxicities, which is not the case for fosfomycin. Let us see fosfomycin's potential role in this context.

1) Preventing the emergence of multidrug-resistant microorganisms

Fosfomycin, unlike carbapenems, has not been overused, so that its use can contribute towards decreasing the selective pressure of other broad-spectrum antibiotics, as it does not promote the emergence of MDR microorganisms, and reserving potent antibiotics such as carbapenems for the occasion when other options are lacking. In addition, fosfomycin does not appear to promote the selection of *C. difficil*e [25]. In some cases, penicillin allergies motivate the selection of a carbapenem for the treatment. An added value of fosfomycin is the possibility of employing it instead of carbapenems as an option for patients with penicillin allergies.

Most studies on fosfomycin efficacy have been conducted on urinary tract infection, because despite fosfomycin's suboptimal oral bioavailability (which is improved in the trometamol formulation), it reaches high concentrations in urine. However, fosfomycin presents good penetration in tissues such as the central nervous system, lung, abscesses, bone and soft tissue, as well as in urine. Although the intravenous formulation has been available in Europe and Japan, it is not available in the US, and therefore the publications that document its efficacy are case-series or case-reports [26]. A clinical trial (ZEUS) is currently ongoing to assess the efficacy of intravenous fosfomycin versus piperacillin/tazobactam in complicated urinary tract infection (Available at https://clinicaltrials.gov/ct2/show/NCT02753946).

There is increasing evidence in favor of the safety and efficacy of intravenous fosfomycin for treating other systemic infections, even in critically ill and immunocompromised patients [27-29].

2) Treating multidrug-resistant microorganisms

The scarcity of new drugs for treating MDR microorganisms is a public health problem, and it is imperative that we find options. The use of old drugs such as fosfomycin can offer a short-term solution [7]. Fosfomycin is frequently active against multidrug-resistant enterobacteria and even extremely drug-resistant enterobacteria, with greater activity against *E. coli* than against *Klebsiella, Enterobacter* and *Pseudomonas*.

To assess fosfomycin's potential as a carbapenem-sparing drug, a clinical trial [30] is currently underway that is attempting to remedy the lack of data regarding the development of fosfomycin resistance during therapy and its impact on colonization by MDR Gram-negative bacilli. This study will compare the efficacy of intravenous fosfomycin versus meropenem for treating bacteremic urinary tract infection by ESBL *E. coli*. There is also the option of oral sequential therapy with fosfomycin trometamol (once the source has been controlled and the bacteremia has been eliminated), providing a basis for using fosfomycin as an alternative to meropenem for this type of infection.

The data on fosfomycin's clinical efficacy for treating infections by carbapenemase-producing bacteria are limited [28, 31]. Fosfomycin susceptibility varies by geographical region [32], although the fact that the MIC cutoff is not universally accepted contributes to the confusion. Fosfomycin resistance is still scarce in Europe but is remarkable in a number of Asian countries [33]. It is interesting to note that up to 94% of New Delhi metallo-beta-lactamase carbapenemase-producing strains (for which the therapeutic arsenal is especially scarce) are susceptible to fosfomycin [34, 35]. Fosfomycin has also been shown to be effective against strains that produce mcr-1, the plasmid that encodes the colistin resistance gene. Fosfomycin's susceptibility is greater in *E. coli* than in *Klebsiella* [36]. To treat urinary tract infections by carbapenemase-producing bacteria, oral fosfomycin trometamol has been employed at high dosages (3 g/48 h x 3 d) [37].

Due to the risk of resistance appearing during treatment, fosfomycin's use in monotherapy is not generally recommended; however, fosfomycin's synergy with antibiotics from other families enables the administration of these antibiotics at lower and less toxic dosages (especially aminoglycosides, glycopeptides and polymyxin B) [5]. Furthermore, fosfomycin represents an alternative to nonnephrotoxic antibiotics, given that fosfomycin also presents synergy with carbapenems (even in some carbapenem-resistant strains). As has been stated earlier for Gram-positive microorganisms, fosfomycin provides protection from the renal toxicity of aminoglycosides in animal models [38]. In any case, when the use of fosfomycin in combination is planned, a synergy test should be performed, given that cases of unpredictable antagonism have been reported [39].

The emergence of fosfomycin resistance in *Pseudomonas aeruginosa* is more common than in *E. coli*, even in combined therapies, and, unlike *E. coli*, does not entail a reduction in bacterial fitness [40]. A number of authors therefore do not recommend using fosfomycin for infections by *Pseudomonas aeruginosa*. However, the O12 serotype, which is usually associated with a resistant phenotype, is more susceptible than others to fosfomycin. There are favorable clinical experiences

in treating respiratory infections by MDR *Pseudomonas*, especially in patients with respiratory exacerbations of cystic fibrosis, in which fosfomycin's efficacy in biofilms contributes [41], as well as in ventilator-associated pneumonia, although there are no randomized clinical trials on this issue [42].

In summary, fosfomycin is an antibiotic with potential for use in ASP given its bactericidal activity, good tolerance, good tissue penetration, absence of induction of MDR microorganisms and its activity against ESBL-producing and carbapenemase-producing enterobacteria. Fosfomycin even has activity against some types with no other available effective antibiotics and can act synergistically with other antibiotics.

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