

## Current key topics in fosfomycin

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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 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 glycylyclines (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<sub>90</sub>) of ESBL *E. coli* strains is typically

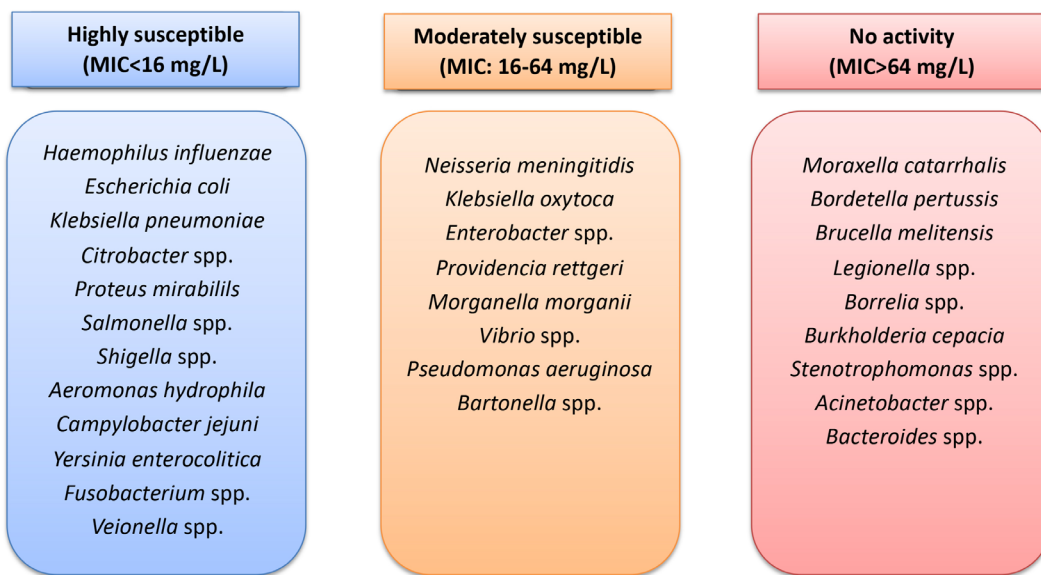


Figure 1 | Susceptibility to fosfomycin of Gram-negative bacteria

2-4 mg/L, although Asian countries have observed greater resistance (MIC<sub>90</sub> 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<sub>90</sub> 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-Avil 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-7* 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 re-

sistance 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 consensus 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 success-

fully 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  $\leq 8$  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  $\leq 8$  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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