

Fosfomycin: Use Beyond Urinary Tract and Gastrointestinal Infections

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The shortage of new antimicrobial agents has made the scientific community reconsider the potential value of old antibiotics. A search of the literature was performed to compile relevant evidence regarding the effectiveness and safety of fosfomycin for the treatment of patients with gram-positive and/or gram-negative bacterial infections (excluding urinary tract infection and gastrointestinal infection). Of 1311 potentially relevant studies, 62 studies were reviewed in detail. Of 1604 patients with various gram-positive and gram-negative infections of various body sites (including pneumonia and other respiratory infections; osteomyelitis; meningitis; ear, nose, and throat infections; surgical infections; obstetric and gynecological infections; arthritis; septicemia; peritonitis; cervical lymphadenitis; eye infections; diabetic foot infections; and typhoid fever) being treated with fosfomycin alone or in combination with other antibiotics, cure was achieved in 1302 (81.1%) of the patients, and improvement was noted in 47 (2.9%). In comparative perioperative prophylaxis trials that included a total of 1212 patients (mainly patients undergoing colorectal surgery), the fosfomycin-metronidazole combination led to results that were similar to those achieved with the combination of other antibiotics (doxycycline, ampicillin, or cephalothin) and metronidazole. In an era in which there is a shortage of new antibiotics, fosfomycin might be considered to be an alternative treatment agent for infections caused by gram-positive and gram-negative bacteria, in addition to its traditional use in treating uncomplicated urinary tract and gastrointestinal infections. Further research on the *in vitro* antimicrobial activity of fosfomycin, especially against multidrug-resistant pathogens (such as extended-spectrum β -lactamase-producing and/or metallo- β -lactamase-producing enterobacteriaceae and *Pseudomonas aeruginosa*, and on the effectiveness and safety of the drug in the treatment of patients with such infections may be warranted.

The continuously increasing problem of antibacterial resistance is well understood and much feared for its potential consequences. Clinicians often face problems in choosing appropriate antibiotic therapy for treating infections caused by gram-positive and gram-negative bacteria, because these pathogens are often resistant to several classes of antibiotics. Drug-resistant bacteria, such as methicillin-resistant *Staphylococcus aureus* and multidrug-resistant *Pseudomonas*, *Acinetobacter*, and *Klebsiella* species, have been frequently isolated from patients with serious infections and are associated with a considerable mortality rate. These facts created the need to discover new effective treatment solutions or even reevaluate and reintroduce already existing

therapeutic agents, such as colistin [1], for addition to the list of the few remaining antibiotics used for treating infections caused by drug-resistant bacteria.

Fosfomycin, a phosphonic acid derivative (cis-1,2-epoxypropyl phosphonic acid), was initially described and isolated in 1969 from cultures of *Streptomyces* species [2]. Today, fosfomycin tromethamine, a soluble salt with improved bioavailability over fosfomycin, is being synthetically prepared and is approved for the treatment of uncomplicated urinary tract infections (UTIs) caused by *Escherichia coli* and *Enterococcus faecalis*. In some countries, such as Japan, Spain, Germany, France, Brazil, and South Africa, fosfomycin has been used extensively for >20 years [3], and in the United States, a related product has been available for oral therapy of uncomplicated UTI (marketed under the brand name Monurol [Inpharzam] and consisting of a sachet containing 5.61 g of fosfomycin tromethamine, equivalent to 3 g of fosfomycin). In Europe, the tromethamine derivative and fosfomycin calcium for oral use, as well as fosfomycin disodium for intravenous use, are avail-

Received 30 March 2007; accepted 29 October 2007; electronically published 21 February 2008.

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Clinical Infectious Diseases 2008;46:1069–77

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1058-4838/2008/4607-0018\$15.00

DOI: 10.1086/527442

able and marketed under different brand names (in Spain, for example, the drug is available as 500-mg fosfomycin calcium capsules, a 1-g fosfomycin disodium ampule for intramuscular injection, and 1-g and 4-g fosfomycin disodium ampules for intravenous use [Fosfocina; Laboratorios ERN]) [4]. Fosfomycin has a bactericidal mechanism of action. It inhibits uridine diphosphate–GlcNAc enol-pyruvyltransferase (MurA) [5]; use of a-glycerophosphate and glucose–6-phosphate active-transport bacterial system is necessary to achieve membrane lysis of the targeted pathogen, while minimizing the possibility of cross resistance with other antibiotics [6].

This review of the available published evidence using PubMed and Scopus databases (searched for the period from November 1971 through January 2007) focuses on the evaluation of the effectiveness and safety of fosfomycin for treating infections (other than urinary tract and gastrointestinal infections) caused by gram-positive and gram-negative bacteria to offer clinicians information for a possible alternative therapeutic treatment regimen for infections of various types. Studies, including case reports and clinical trials written in English, German, or French, were reviewed and included data for patients of all ages (from infants to elderly individuals) with various diseases (excluding UTIs and gastrointestinal infections).

IN VITRO ACTIVITY

Fosfomycin has a broad-spectrum activity against gram-positive and gram-negative bacteria. Breakpoints to define resistance for licenced use differ: ≥ 256 mg/L, according to the Clinical and Laboratory Standards Institute [7], >128 mg/L according to the British Society for Antimicrobial Chemotherapy [8], and >32 mg/L according to the Committee on Antibiograms of the French Society of Microbiology [9]. It has in vitro activity against *S. aureus* (MIC₅₀, 8 mg/L; MIC₉₀, 16mg/L) [10], *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, and *E. faecalis*. *Listeria monocytogenes* is resistant to fosfomycin, whereas other *Listeria* species (e.g., *Listeria ivanovii*) may be susceptible [11]. Fosfomycin shows very good activity against many gram-negative bacteria, such as *E. coli*, *Proteus* species, *Klebsiella pneumoniae*, *Enterobacter* species, *Serratia marcescens*, and *Salmonella typhi*. *Pseudomonas aeruginosa* (MIC₅₀, 32mg/L; MIC₉₀, 64mg/L) [12] exhibits considerable rates of resistance. However, a combination of fosfomycin and another antibiotic (cefepime, aztreonam, or meropenem) was effective in an in vitro study involving *P. aeruginosa* clinical isolates from sputum, urine, and blood samples [13]. *Acinetobacter baumannii* is resistant to fosfomycin [14], although in vitro combinations of fosfomycin with aminoglycosides may be synergistic [15]. *Bacteroides fragilis* is resistant to fosfomycin.

PHARMACOLOGICAL CHARACTERISTICS

Fosfomycin has a low molecular weight and a relatively long half-life (mean half-life \pm SD, 5.7 ± 2.8 h) and, therefore, penetrates various tissues with ease, achieving the MICs needed to inhibit the growth of most pathogens. More precisely, results from clinical trials involving patients with soft-tissue infection [16, 17] have shown that fosfomycin achieves good penetration in inflamed tissues. Similarly, fosfomycin has been shown to have excellent diffusion in both the aqueous humour and vitreous body of patients scheduled to undergo cataract surgery [18, 19], as well as in the CSF of patients with meningitis [20, 21]. When fosfomycin is administered intravenously at 8 g every 8 h, mean values (\pm SD) of the area under the concentration-time curve for the dosing interval of 8 h were 929 ± 280 mg \times h/L and 225 ± 131 mg \times h/L for plasma and CSF, respectively, after a single-dose intravenous administration of 8 g of fosfomycin ($P < .03$). The mean ratio (\pm SD) of the area under the concentration-time curve for CSF to the area under the concentration-time curve for plasma was 0.23 ± 0.07 after a single dose and 0.27 ± 0.08 after multiple doses ($P > .05$). At steady state, the time above MIC ($t > \text{MIC}$) values were 98%, 92%, and 61% for pathogens with MIC values of 8 mg/L, 16 mg/L, and 32 mg/L, respectively [22]. Also, the fact that fosfomycin uses an active transport system for its entry into the cells may prove to be helpful for the treatment of patients with diseases such as chronic granulomatosis [23].

The form of the medication for intravenous use is fosfomycin disodium; this is associated with a high sodium intake that could be a limitation in patients with heart failure or who are receiving hemodialysis. Transformation to metabolites has not been noted, and the medication is excreted unchanged in the urine. No tubular secretion occurs. In 5 anuric patients undergoing hemodialysis, the half-life of fosfomycin trometamol during hemodialysis was 40 h. In patients with varying degrees of renal impairment (creatinine clearance range, 7–54 mL/min), the half-life of fosfomycin increased from 11 h to 50 h, and the percent of fosfomycin recovered in urine decreased by approximately two-thirds (from 32% to 11%) [24].

DRUG INTERACTIONS

Scarce data from in vivo studies regarding drug interactions of fosfomycin are available. Metoclopramide reduces the bioavailability of fosfomycin [25], whereas cimetidine has no effect.

ADVERSE EFFECTS

A low rate of adverse events, mainly associated with the gastrointestinal tract and the skin, was reported in the reviewed studies. Adverse events, such as mild gastrointestinal disturbances, did not necessitate discontinuation of treatment [26,

27], except in 2 patients with severe nausea and neutropenia [28, 29]. In some other patients, local phlebitis [30], pain at injection site (mostly seen in patients who received intramuscular administration) [27, 31, 32], and eosinophil count changes were either tolerable or transient. In addition, experimental studies have supported the finding that fosfomycin confers a protective effect when coadministered with cisplatin, therefore reducing its possible ototoxicity and nephrotoxicity [33].

It is interesting that fosfomycin seems to be relatively well tolerated by neonates and children, even after several months of administration [34], resulting in improvement or cure of the infection. In another study [35], fosfomycin was administered for 14–28 days to 24 children with *S. marcescens* septicemia, leading to cure of the infection in 21 (87.5%) of 24 children without any significant adverse events reported.

CLINICAL USE

Of 1311 studies that we identified as being potentially relevant, 62 were reviewed in detail to evaluate the effectiveness and safety of fosfomycin for infections caused by gram-negative and gram-positive bacteria (excluding UTIs and gastrointestinal infections).

Seventeen case reports—mostly from France, Spain, Germany, and Japan—were identified for the period 1977–2006 [36–52]. Six cases involved children aged ≤ 17 years, whereas the rest of the patients were adults aged 18–69 years. Fosfomycin was used for the treatment of meningitis in 4 patients [40, 47, 50, 51], endocarditis in 2 patients [40, 48], eye infection in 2 patients [36, 39], postoperative infection in 2 patients [45, 46], and encephalitis [42], shunt infection [48], blood stream infection [44], acute enteritis [37], glomerulonephritis [43], prostatitis [38], and pulmonary infection [52] in 1 patient each. The most common gram-positive and gram-negative pathogens involved were *S. aureus* and *P. aeruginosa*, respectively. In 7 cases [36, 37, 41, 45, 47, 49, 52], fosfomycin was given to patients on primary intention or according to susceptibility testing results, whereas it was administered to the remaining 10 patients after failure of the previously administered antibiotics to achieve resolution of the infection. Fosfomycin was administered intravenously (1–16 g daily, administered in divided doses every 6–8 h) for a maximum of 60 days; in the majority of cases, it was administered in combination with other antibiotics (ceftriaxone, cefotaxime, cefoperazone, ciprofloxacin, gentamicin, amikacin, vancomycin, aztreonam, rifampin, or sulbactam). No major adverse events were reported by any of the patients, although erythema and pain at the injection site were noted in 1 case [52]. Resolution of infection was achieved in 15 (88.2%) of the 17 cases, improvement was achieved in 1 (5.9%) [52], and treatment failure was experienced in 1 (5.9%) [40]. All patients were stable, without any

relapse or development of complications in the studies that reported follow-up data (follow-up periods ranged from 1 month to 24 months).

Nine relevant case series were also reviewed [34, 53–60]; the majority were from France (including 11 patients with gram-negative infections [34, 53] and 47 patients with gram-positive infections). There were 47 male and 11 female patients; of these patients, 34 were children (age, 8 months to 14 years), and 24 were adults (age, 21–83 years). Fosfomycin was administered to 22 patients with meningitis [53, 57, 58, 60] and 9 with endophthalmitis [56]; in some cases, the infection occurred after an operation or trauma. Fosfomycin was administered to treat pulmonary infections in 8 patients with cystic fibrosis [61], septicemia in 7 patients [55], endocarditis in 5 patients (3 of whom developed the infection after pacemaker implantation) [54], venticulitis in 5 patients [59], and arthritis in 2 patients [53]. The major pathogens were *P. aeruginosa*, *S. aureus*, and *S. epidermidis*. The reason for fosfomycin administration was treatment failure in 14 of 26 patients who had received previous antibiotics [34, 53, 54, 59]. The rest of the patients were given fosfomycin on the basis of the therapeutic treatment protocol or susceptibility test results. In 50 of the 58 patients included in these case series, fosfomycin (1–16 g daily, administered in divided doses every 6–8 h) was administered intravenously in combination with other antibiotics, such as aminoglycosides, penicillins, and cephalosporins; the mean duration of therapy was 12.3 days, excluding 8 patients with cystic fibrosis who received treatment for longer periods [34]. The overall cure rate in these case series was 77.6% (45 of 58 patients experienced cure). No adverse effects were reported [34].

In table 1, 31 studies [26–32, 62–85] presenting data regarding the effectiveness and safety of fosfomycin for the treatment of various gram-positive and gram-negative infections in hospitalized patients are included. Most studies originated from Spain and France, followed by Germany and Austria. In total, 1529 patients who received fosfomycin are included in these studies; of these patients, 174 had previously received antibiotics (penicillins, cephalosporins, tetracycline, ciprofloxacin, clindamycin, or chloramphenicol) that did not lead to the resolution of the infection [27, 30, 62–64, 79, 85], 92 had previously undergone a neurosurgical [72, 75] or other [30, 71] kind of operation, and 39 were trauma patients [78]. The most commonly isolated pathogens were *Staphylococcus* species, *Streptococcus* species, *P. aeruginosa*, *Enterobacter* species, *Klebsiella*

Table 1. Cohort descriptive studies regarding use of fosfomycin for the treatment of various gram-negative and gram-positive infections.

The table is available in its entirety in the online edition of *Clinical Infectious Diseases*.

species, *E. coli*, *Proteus* species, and *S. typhi*. These pathogens caused a wide range of infections, including pneumonia and other respiratory infections [28, 66, 71, 73, 76, 77, 80–84]; osteomyelitis [27, 29, 30, 65, 68, 78, 81, 84]; meningitis [70, 72, 75, 84]; ear, nose, and throat infections [32, 62, 73, 74, 84]; surgical infections [79, 83, 84]; obstetric and gynaecological infections [31, 84, 85]; arthritis [68, 75]; septicemia [69, 84]; peritonitis [67]; cervical lymphadenitis [64]; eye infections [84]; diabetic foot infections [63]; and typhoid fever [26]. Fosfomycin was administered to patients via the oral, intravenous, or intramuscular route or in a combination of routes at a dosage of 2–24 g daily, administered in divided doses every 6–8 h. In the studies that provided relevant data, the mean duration of fosfomycin treatment ranged from 5 to 21 days, including fosfomycin administered alone or in combination with other antibiotics, such as cefotaxime, ceftriaxone, penicillin, ampicillin, amoxicillin, clindamycin, gentamicin, or ciprofloxacin. More than 192 patients required surgical procedures in addition to fosfomycin treatment [27, 29, 30, 32, 62–65, 70, 72, 78, 79].

The overall cure rate for fosfomycin in the studies reviewed in table 1 was 81.2% (1242 of 1529 patients experienced cure), whereas improvement was noted in 2.9% (46 of 1529 patients). Overall, including patients reported in the case reports and the case series, as well as in the studies included in table 1, 1604 patients received fosfomycin, and the cure rate was 81.1% (1302 of 1604 patients experienced cure), whereas 2.9% (47 of 1604 patients) showed improvement.

A relatively good tolerance to fosfomycin was reported by patients in most of the studies providing relevant data: 36 (5.4%) of 664 patients reported mild gastrointestinal symptoms (e.g., nausea, diarrhea, epigastralgia, and vomiting); 27 (4.0%) of 664 developed skin manifestations (e.g., rash, dermatitis, and exanthema); 20 (3.0%) of 664 experienced pain at the injection site or phlebitis; and 14 (2.1%) of 664, 8 (1.2%) of 664, and 1 (0.1%) of 664 patients showed moderate increases in platelet count, eosinophil count, and transaminase levels, respectively.

In table 2, data from 5 studies regarding prophylactic use of fosfomycin are presented [78, 86–89]. Four of these studies were randomized trials (3 from Sweden and 1 from Denmark) and involved 1212 patients who underwent elective colorectal operations [86–89]. Fosfomycin (8 g daily administered intravenously) and metronidazole were given preoperatively to 612 patients [86–89] and continued for a maximum of 3 days postoperatively; metronidazole and doxycycline, cephalothin, bacitracin-neomycin, or ampicillin were given to 600 patients and continued postoperatively for a period similar to that for fosfomycin. Of the 612 patients who received the fosfomycin-metronidazole combination, 29 (4.7%) developed infective complications (deep, abdominal, or wound infections or septicemia). Of the 600 patients who received prophylaxis with antibiotics other than fosfomycin, 43 (7%) developed infective

complications. With respect to pneumonia, in the only study that provided relevant data [87], 13 (5%) of 259 patients who received the fosfomycin combination treatment and 5 (2%) of 258 patients who received other treatments developed this nosocomial infection after undergoing operations. In total, 17 patients died, 4 of whom died due to infective complications (2 in the fosfomycin group and 2 in the comparator group), and mild adverse events were reported. Finally, the fifth study reported in table 2 [78] involved 60 traumatized patients who were not treated surgically for their fractures (no fractures were reported as open). After fracture reduction was done, fosfomycin was given prophylactically as monotherapy (2–4 g daily) either orally or intramuscularly in all the patients; no infective complications were reported.

The evidence gathered from the reviewed studies suggests that fosfomycin may be used as an alternative prophylactic or therapeutic agent for infections caused by various gram-positive and gram-negative bacteria. One has to acknowledge that the majority of the studies in this review are open and/or non-comparative. In addition to the studies that we reviewed in detail, favorable results with respect to the effectiveness and safety of fosfomycin were provided from several clinical trials conducted in Japan [90]. Specifically, the oral form of fosfomycin proved to be effective for 912 (76%) of 1200 patients, whereas the parenteral form was effective for 340 (68%) of 500 patients who received fosfomycin for the treatment of several gram-positive and gram-negative infections. Also, fosfomycin has been administered as a nebulized treatment in 28 patients with chronic sinusitis [91], diminishing the symptoms of 22 (78%) of 28 patients to various degrees.

Taking into account the increasing problem of antimicrobial resistance worldwide and the fact that the success of treatment with fosfomycin reported in the reviewed studies was mostly among patients treated during previous decades, it is possible that fosfomycin may not be as effective today as it was in the past. However, fosfomycin has proved to be clinically useful in the treatment of infections due to various multidrug-resistant bacteria, such as penicillin-resistant pneumococci, methicillin-resistant *S. aureus*, vancomycin-resistant enterococci (mainly *E. faecalis*; *Enterococcus faecium* susceptibility ranges widely, from 0% [92] to 67% [93]), and extended-spectrum β -lactamase-producing enterobacteriaceae [94]. In most of these infections, the drug is given in combination with another antibiotic.

DEVELOPMENT OF DRUG RESISTANCE

Data from in vitro studies show that a drawback of fosfomycin is that it can be associated with the development of drug resistance [95]. However, clinical studies involving the use of fosfomycin to treat UTI show that, in countries where the medication has been used for many years, ~3% of various

Table 2. Studies regarding prophylactic use of fosfomycin.

Study, country, year of publication	Study design	No. of patients	Operation	No. of patients receiving prophylactic antibiotics, by regimen		No. (%) of patients with infection, by regimen		Findings at follow-up (duration of follow-up, months)	Adverse effect (no. of patients)
				Regimen 1	Regimen 2	Regimen 1	Regimen 2		
Olsson-Liljequist et al. [62], Sweden, 1993	Multicenter, double-blind, randomized trial	511 enrolled, 488 evaluated	Elective colorectal surgery	First infusion: at induction of anesthesia, 251/488 received fosfomycin-metronidazole; second infusion: 8 h later, 251/488 received fosfomycin 8 g IV	First infusion: at induction of anesthesia, 237/488 received doxycycline-metronidazole; second infusion: 8 h later, 237/488 received placebo	5/251 (2)	13/237 (5.5)	NA	NA
Andaker et al. [63], Sweden, 1992	Multicenter, double-blind, randomized trial	559 enrolled, 517 evaluated	Elective colorectal surgery	First infusion: before operation, 259/517 received fosfomycin-metronidazole; second infusion: 8 h later, 259/517 received fosfomycin 8 g IV	First infusion: before operation, 258/517 received doxycycline-metronidazole; second infusion: 8 h later, 258/517 received placebo	Abdominal infection, 12/259 (4.6); pneumonia, 13/259 (5)	Abdominal infection, 19/258 (7.4); pneumonia, 5/258 (2)	Regimen 1: 5 patients died, including 1 due to infective complications; regimen 2: 5 patients died, including 1 due to infective complications (1)	Nausea (3), urticaria (2), purpura (1), thrombophlebitis (1)
Nohr et al. [64], Denmark, 1990	Prospective double-blind randomized controlled trial	244 enrolled, 149 evaluated	Elective colorectal surgery	3 days before operation, 72/149 received placebo; 1 h before operation, 72/149 received fosfomycin-metronidazole 8 g IV	2 days before operation, 77/149 received bacitracin-neomycin; 1 day before operation, 77/149 received metronidazole; 1 h before operation, 77/149 received ampicillin	Infective complications, 9/72 (12.5)	Infective complications, 8/77 (10.4)	Regimen 1: 5 patients died, including 1 due to infective complications; regimen 2: 2 patients died, including 1 due to infective complications (1)	Nausea, vomiting
Lindhagen et al. [65], Sweden, 1981	Comparative randomized study	58	Elective colorectal surgery	1-3 h before operation until 3 days after operation, 30/58 received fosfomycin-metronidazole 8g daily IV	1-3 h before operation until 3 days after operation, 28/58 received cephalothin-metronidazole	Surgical septic complications, 3/30 (10)	Surgical septic complications, 3/28 (10)	NA	None
Hernandez Casado et al. [50], Spain, 1977	Retrospective study	60	Traumatized patients did not undergo operations but were given fosfomycin after fracture reduction	60/60 received fosfomycin 2-4 g daily PO or IM (mean duration, 4 days)	None	No patient developed complications or intolerances or toxic effects	NA	NA	NA

NOTE. IM, intramuscularly; IV, intravenously; PO, per os.

bacterial pathogens are resistant to fosfomycin, and this percentage has practically remained the same for several years [96]. It has been postulated that resistance to fosfomycin entails a biological cost (i.e., that the pathogenic strains are less fit) [97]. Even in infections other than UTIs, fosfomycin has preserved its value in some countries; in other countries, despite the presence of other effective therapeutic regimens, combinations involving fosfomycin remain clinically useful [98].

In infections other than UTIs, a mean incidence of 3% resistance development was reported (10% for *P. aeruginosa* [84]). It is interesting to note that, in studies in which fosfomycin has been used for surgical prophylaxis, an 8% emergence of resistance to fosfomycin was noted in aerobic fecal gram-negative bacteria, but no resistance was noted among strains causing infection after elective colorectal surgery; this suggested that emerging resistance to fosfomycin may be associated with less biological fitness [86]. The pathogens that were most frequently found to develop resistance during treatment were *P. aeruginosa* and *Klebsiella* species.

In the studies that we reviewed in detail and which are included in table 1 [26–32, 62–85], resistance to fosfomycin was noted in a total of 39 (10.8%) of 360 patients; it referred to various pathogens, including coagulase-negative *Staphylococcus* species, *P. aeruginosa*, *Klebsiella* species, and *Enterobacter* species. In addition, 2 patients developed superinfections due to *P. aeruginosa* and *Enterobacter cloacae* that were resistant to fosfomycin and ceftriaxone [70].

The development of resistance is probably one of the reasons why clinicians have used the medication mainly as a combination therapy, rather than as monotherapy [99]. In addition, fosfomycin usually exhibits in vitro synergism with other classes of antibiotics, such as β -lactams against *S. aureus*, coagulase-negative *Staphylococcus* species, *S. pneumoniae*, and *P. aeruginosa* [13, 94, 99]; however, at times, antagonism or indifference has been noted with such combinations [99, 100, 101].

A study investigating mechanisms of resistance of *P. aeruginosa* isolates to fosfomycin showed that, first, the presence of adenosine triphosphate accelerated the inactivation of fosfomycin by *P. aeruginosa* and, second, there was no strong evidence proving transfer of resistance via plasmids, although further research is needed on the exact mechanism of resistance, because it is not yet clearly understood [102]. On the other hand, a *P. aeruginosa* strain was the pathogen responsible for an outbreak in an intensive care unit and was found to be susceptible only to fosfomycin, amikacin, and polymyxin B [103]. In addition, intravenous fosfomycin has proved to be successful in treating multidrug-resistant *P. aeruginosa* in patients with cystic fibrosis [28]. It is also noteworthy that fosfomycin has excellent in vitro activity against extended-spectrum β -lactamase *K. pneumoniae* and *E. coli* [104, 105], although mutators may arise [106]. These facts highlight the

need for further research on the susceptibility of gram-negative pathogens to fosfomycin [107].

SUMMARY

Fosfomycin is a bactericidal agent showing low levels of toxicity as well as a low level of cross-resistance with other antibiotics. We believe, based on the available evidence from clinical and other studies included in this review, that further research on the in vitro antimicrobial activity of fosfomycin, especially against multidrug-resistant pathogens, and on the effectiveness and safety of the drug in the treatment of patients with such infections may be warranted. This old antibiotic, which has practically been abandoned in several parts of the world, may be considered as an alternative agent (if shown to be active by in vitro antimicrobial susceptibility testing) for the treatment of infections in various sites due to gram-positive and gram-negative bacteria, especially in cases involving multidrug-resistant pathogens in which previous antibiotics have failed to cure the infection or when patients are intolerant to the antibiotics considered as first-line treatment agents.

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

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