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REVIEW

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Intravenous fosfomycin for the treatment of patients with bone and joint infections: a review

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ABSTRACT

Introduction: Fosfomycin is a wide spectrum bactericidal antibiotic with a unique mode of action, low toxicity, and good penetration in tissues with deep-seated infections, including bone and joint infections.

Areas covered: Data were extracted from 19 published articles. Three hundred and sixty-five patients, with broad age range, received intravenous fosfomycin for the treatment of bone and joint infections (including arthritis, acute and chronic osteomyelitis, discitis, periprosthetic joint infection). Fosfomycin was given as part of a combination antimicrobial therapy in the majority of patients (93.7%). The dosage of fosfomycin ranged from 4 g/day (in one case) to 24 g/day. The dosage of fosfomycin, in some cases, mostly pediatric, was calculated based on body weight, ranging from 50 mg/kg/day to 250 mg/kg/day. The duration of fosfomycin treatment ranged from a couple of days up to 3 months. The most common isolated pathogen was *Staphylococcus aureus* (38.9%). Three hundred patients (82.2%) were successfully treated. Fosfomycin was well tolerated, as few patients developed mild adverse events, mostly gastrointestinal discomfort, hypernatremia, skin rash, and neutropenia.

Expert opinion: The available data suggests that intravenous fosfomycin may be beneficial for the treatment of patients with bone and joint infections, especially when used as part of a combination antibiotic regimen.

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Fosfomycin; bone and joint infections; osteomyelitis; arthritis; discitis; combination

1. Introduction

1.1. Bone and joint infections

Bone and joint infections represent a great variety of osteoarticular infections, including septic arthritis, osteomyelitis, spinal infections (discitis, vertebral osteomyelitis), prosthetic joint infections and diabetic foot osteomyelitis. They may be caused by pathogens that affect the bones and joints, either hematogenously (most often in children and the elderly) or by direct infection of the region, including post-operative and post-traumatic inoculation [1].

They require immediate and targeted treatment because they may cause permanent disability, or even death, if left without the appropriate approach. In some cases, surgical and antimicrobial treatment must be implemented simultaneously, while in others, antibiotics alone may be sufficient. The choice of the correct antibiotic regimen, either empiric or guided by tissue or blood cultures' results, is crucial. Bone and joint infections require prolonged course of antibiotic treatment, and antimicrobials that can penetrate into the osseous tissue [2].

The treatment of bone and joint infections is often challenging. They require antibiotics that have both satisfactory penetration into the osseous tissue and are effective against a wide range of pathogens, including multidrug-resistant bacteria (MDR) and extensively drug-resistant bacteria (XDR). In this context, the evaluation of the effectiveness and safety of intravenous fosfomycin is of interest, as this antibiotic could be a valuable agent for the treatment of patients with bone and joint infections.

1.2. Fosfomycin

Fosfomycin is the only phosphonic acid derivative developed for clinical practice since 1970s [3]. Its physicochemical profile with a relatively low molecular weight (138 Da) and characteristic hydrophilic properties, combined with its negligible binding to plasma proteins, offers a broad distribution into several tissues [4]. Its bactericidal action is achieved by irreversible inhibition of an early stage of the bacterial cell wall synthesis. Fosfomycin is active against a broad spectrum of both Gram-positive and Gram-negative pathogens including multiple resistant bacteria, such as extended-spectrum beta-lactamase-producing (ESBL) and/or carbapenemase-producing enterobacteria, methicillin-resistant *Staphylococcus aureus* (MRSA), and penicillin-resistant *Streptococcus pneumoniae* [5–9].

Experimental studies showed that fosfomycin has high activity against staphylococcal, enterococcal and ESBL-producing *E. coli* biofilms, particularly in combination with other antibacterials [10–12]. In addition, fosfomycin exerts

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Article highlights

- Fosfomycin has strong antimicrobial activity against many bacterial pathogens and is considered for various types of infections including staphylococcal, enterococcal and ESBL-producing *E. coli* biofilms, particularly in combination with other antibacterials
- The use of intravenous fosfomycin has been recently revised, because the antibiotic has favorable pharmacokinetic characteristics, low toxicity and high tissue penetration, even in deep-seated infections, like bone and joint infections.
- A critical evaluation of the availale evidence showed that 300 of 365 patients (82.2%) who received intravenous fosfomycin, alone or in combination with another antibiotic, for the treatment of bone and joint infections were succesfully treated.
- Intravenous fosfomycin may be beneficial for empiric and targeted first-line treatment of patients with bone and joint infections. Also, it is a therapeutic option in patients with bone and joint infections when there is failure of initial antibiotic therapy or concurrent presence of difficult-to-treat pathogens.

bactericidal activity against intracellular persisting bacteria, e.g. *Staphylococcus aureus* [13]. Another useful effect is its broad synergistic effect with other antibiotics, including beta-lactams, given its unique mode of action [14]. As severe bone infections are often complicated by factors such as abscess formation and tissue hypoxia which render bacteria more tolerant to most antibiotics, fosfomycin´s higher antimicrobial activity under low oxygen conditions and low pH and sufficient penetration into abscess fluid may be beneficial for treatment of these difficult-to treat-infections [15–18].

Regarding the bone tissue, fosfomycin seems to achieve relatively high bone concentrations compared with other antibiotics possibly due to its chemical structure similarity with hydroxylapatite, promoting distribution into the inorganic part of bone [19]. A crucial step in order to achieve therapeutic efficacy against bone and joint infections is to ensure adequate antibiotic concentrations into the site of infection [20]. Studies in rats provide information regarding the penetration of fosfomycin into the infected bone tissue. One study of experimental MRSA osteomyelitis model in 11 rats showed that 7 out of 9 bone specimen cultures did not grow any pathogen when treated with fosfomycin [21]. Similarly, in another study, fosfomycin eradicated MRSA in 8 out of 10 bone specimen cultures of rat-models with osteomyelitis [22].

A human study included eight patients with deep-seated bacterial foot infection. Fosfomycin penetrated well into osseous tissue and equilibrated fully with plasma at 3 h post-infusion. After a single intravenous dose of approximately 100 mg of fosfomycin per kg of body weight, the mean C_{max}, $T_{max,}$ and AUC_{0-6} for bone were 96.4 mg/L, 3.9 h and 330.0 mg · h/L, respectively. The degree of tissue penetration as determined by the ratios of the AUC_{0-6} for bone to plasma was 0.43 ± 0.04 [23].

A recently published pharmacokinetic study in patients with osteoarticular infections suggests adequate probability of target attainment of fosfomycin dosages of 12–20 g/day for pathogens with MIC values up to 128 mg/L assuming a time-dependent antimicrobial activity [24]. Moreover, a relatively extended post-antibiotic effect (PAE) of fosfomycin against strains of *E. coli* and *P. mirabilis* has been reported, ranging between 3.4 h and 4.7 h [25].

The use of intravenous fosfomycin has been recently revised, as it has favorable pharmacokinetic characteristics, low toxicity, and high tissue penetration, even in deep-seated infections, like bone and joint infections. In this context, the use of intravenous fosfomycin for the treatment of patients with bone and joint infections could be considered.

1.3. Objective

The objective of this study was to evaluate the available published data regarding the use of intravenous fosfomycin for the treatment of patients with bone and joint infections.

2. Literature search

Published evidence concerning the use of intravenous fosfomycin for the treatment of bone and joint infections was searched in PubMed, Web of Science, Scopus, and Google Scholar. Terms used for this search included fosfomycin and bone and joint infections (osteomyelitis, discitis, diabetic foot infection, and periprosthetic joint infection). Papers referring to human data were included in the outcome analysis. Data from published papers, including prospective and retrospective studies, case series and case reports that referred to the effectiveness, and safety of intravenous fosfomycin for the treatment of bone and joint infections, were analyzed.

The information presented in this analysis refers to the demographic data of the patients, the specific indications for which intravenous fosfomycin was administered, and the isolated pathogens. Additionally, the dosage of fosfomycin, the duration of administration, the partner of fosfomycin when a combination treatment was used, and the clinical outcome as well as the adverse events of the treatment were all analyzed.

3. Available published evidence

3.1. Relevant published papers

Nineteen published papers are included in this analysis, as they report data on the effectiveness of intravenous fosfomycin for the treatment of bone, and joint infections. They consist of six prospective, three retrospective studies, one case control study, four case series, and five case reports. According to the data of these studies, 365 patients in total received intravenous fosfomycin for the treatment of bone and joint infections. Table 1

3.2. Demographic data – indications

Out of the total 365 patients studied, 144 were children, 129 were adults, whereas for 92 patients there is not clear information on their exact age. Most of the cases studied in this analysis received intravenous fosfomycin for osteomyelitis. Specifically, 296 patients (81.1% of the total patients included

Table 1. Published evidence on the use of intravenous fosfomycin for the treatment of patients with bone and joint infections.

Author, country, year [ref]	Type of study	No. of patients (n) that received intravenous fosfomycin	Age	Pediatric/ Adult	Indication (s)	Isolated pathogens (numbe of patients)	Fosfomycin as first-/second-line line treatment	Antibiotics given with fosfomycin (number of patients)	Fosfomycin daily dose	Fosfomycin dosage regimen	Duration of fosfomycin treatment	Clincal outcome	Adverse events (number of patients)
Badelon et al, France, 1988 [39]	prospective	14	12 days – 13 years (mean: 3.3 y)	pediatric	osteomyelitis arthritis	*S. aureus* and *H. influenzae* (42% of cases)	first-line	cefotaxime	100 mg/kg	100 mg/kg in three doses	15 days	14/14 cured	NA
Corti et al, Switzerland, 2003 [26]	case-control	60	Group 1: fosfomycin alone: mean 7 y (0.08–15 y) Group 2: fosfomycin in combination: mean 6 years (0.08–15.5 y)	pediatric	acute hematogenous osteomyelitis, without primary surgery	Group 1: *S. aureus* (4), CoNegative *Staph.*(3) Group 2: *S. aureus* (11), *CoNegative Staph.* (3), *S. pyogenes* (2), *S. pneumonia* (1)	first-line	Group 1: 23 patients received fosfomycin alone Group 2: 47 patients received fosfomycin with other antimicrobials (flucloxacillin (38) amoxicillin (2), amoxicillin/ clavulanic acid (4), clindamycin (2), gentamycin (1))	200 mg/kg	NA	Group 1: 2.5 weeks Group 2: 3.1 weeks	60/60 cured	Group 1: diarrhea (1) Group 2: fosfomycin with flucloxacillin 10 exanthema (10), diarrhea (1), leukopenia (1)
Dinh A et al, France, 2012 [5]	prospective	32	NA	NA	bone and joint infections	MRCNS (10) KES (7) *E. coli (6) P. aeruginosa*(5) MRSA (4) *Streptococcus* spp.(3) MSSA (3) *A. viridans* (1) *Proteus* (1) *Citrobacter* (1) *Enterococcus* (1), polymicrobial infection (6)	first-line	glycopeptide (10) third generation cephalosporin (9) carbapenem (8) fluoroquinolone (4) methicillin (2) rifampicin (3) metronidazole, cefepime, colistin (1)	12–16 gr	4 gr x 3–4 times/ day	49.3 + 40 days mean 54 days	19/32: favorable outcome, 4/ 32 unfavorable, 1/32: early death, 8/32: lost on follow-up	NA
Fitoussi, F et al, France, 2007 [27]	retrospective	18	9 month – 14 years (mean 6.5 y)	pediatric	hematogenous wrist osteomyelitis	MSSA (7), MRSA (1)	first-line	cefotaxime (7 days) IV, followed by oral antibiotics (18)	NA	NA	7 days IV and 6 weeks in total	15/18 cured 3/18 radiologic abnormalities of the wrist	NA
Gouyon JB et al, France, 1985 [28]	case series	2	newborns	pediatric	osteomyelitis	*Staphylococcus spp.* (2)		cefotaxime (2)	50 mg/kg	NA	mean 12.7 days, (9–14 days)	2/2 cured	hypernatremia (2)
Guggenbichler JP et al, Germany-Austria, 1989 [29]	case series	36	children	pediatric	acute hematogenous osteomyelitis	*S. aureus* (16) *H. influenzae* (2) *Salmonella* (1) *Enterobacter* (1) *S. pneumomiae* (1) unknown (15)		cefamandole IV (36) for 10–14 days, (followed by oral clindamycin for 3–6 weeks)	250 mg/kg	250 mg/kg in three doses	10–14 days	34/36 cured	neutropenia (1)

(*Continued*)

Table 1. (Continued).

Author, country, year [ref]	Type of study	No. of patients (n) that received intravenous fosfomycin	Age	Pediatric/ Adult	Indication (s)	Isolated pathogens (numbe of patients)	Fosfomycin as first-/second-line line treatment	Antibiotics given with fosfomycin (number of patients)	Fosfomycin daily dose	Fosfomycin dosage regimen	Duration of fosfomycin treatment	Clincal outcome	Adverse events (number of patients)
Hernandesz-Casado V, Spain, 1977 [30]	case series	2	adults	adults	osteomyelitis	*S. aureus* (2)	first-line	none	12 g/day IV 4 g/ day IM 4 g/ day PER OS	NA	1 pt (3 days IV, 6 days IM and 14 days per os) 2nd pt (2 days IV, 10 days IM and 20 days per os)	2/2 cured	NA
Meissner A et al, Germany, 1989 [32]	prospective	60	17–76 years (mean 37.4 y)	adults	chronic posttraumatic osteomyelitis	*S. aureus* (34) CoNegative Staph. (15) *S. agalacticae* (4) *E. faecalis* (4) *P. aeruginosa* (10) *P. vulgaris* (2) *P. maltophila* (2) and others (1 each)	second-line	NA	10 g loading dose (5 g in 5 cases) before surgery and then 15 g/ day	10 g loading dose (5 g in 5 cases) before surgery and then 3 × 5 g/ day	5–28 days (mean 13.9 days)	29/60 very good 2/60 good 8/ 60 satisfactory 14/60 relapse of osteomyelitis 7/60 lost to follow-up	allergic exanthema (2) mild gastrointenstinal disorders (4) phlebitis (7)
Portier, H et al, France, 1984 [34]	prospective	10	2.5 months –69 years (7 adults 3 children)	both	bone and joint infections (4 post- traumatic, 2 post – surgery, 2 osteo-arthritis, 1 post-osteosynthesis and 1 osteomyelitis)	*S. aureus* (10) (2 MRSA, 8 penicillinase +), 2 were mulitinfections: 1 *S aureus* penicillinase +, Bacteroides, 1 MRSA with group D *Streptococcus alcaligenes*)		cefotaxime (10)	50 mg/kg	50 mg/kg in three doses	11–21 days (mean 16.5 days)	9/10 cured, 1/10 relapsed	Treatment was discontinued in 3 cases, because of neutropenia and hyperpyrexia, neutropenia (1200/ mm^3) at day 21, increase of alanine-aspartate transaminase at day 15. Cefotaxime was incriminated in these adverse effects since they were reversible after its discontinuation.
Reinehr T et al, Holland, 2000 [35]	case series	11	mean 11 years	pediatric	chronic osteomyelitis	not reported		combination with penicillin (11), followed by oral clindamycin for 3 months	200 mg/kg	NA	mean 21 days	5/5 cured in group A 5/6 cured in group B – 1/6 relapsed 11 months later, but recovered after another course of antibiotics	NA

(*Continued*)

Table 1. (Continued).

Author, country, year [ref]	Type of study	No. of patients (n) that received intravenous fosfomycin	Age	Pediatric/ Adult	Indication (s)	Isolated pathogens (numbe of patients)	Fosfomycin as first-/second-line line treatment	Antibiotics given with fosfomycin (number of patients)	Fosfomycin daily dose	Fosfomycin dosage regimen	Duration of fosfomycin treatment	Clincal outcome	Adverse events (number of patients)
Nakamura et al, Japan, 2020 [33]	case report	1	84 years	adult	vertebral osteomyelitis L2-3 and a psoas abscess	MRSA (1)	second-line – previous treatments: 2 weeks of vancomycin, 2 weeks of daptomycin and 4 weeks of high dose vancomycin with abscess drainge	imipenem/cilastatin (1)	4g	NA	4 weeks	1/1 improvement of the abscess- almost disappeared, CRP within normal range	NA
Lee WS et al, Taiwan, 2016 [31]	case report	1	85 years	adult	osteomyelitis and discitis L4-5, epidural abscess	MRSA (1)	second-line- previously received ertapenem/ vancomycin. Empirical for 4 days: cefoperazone/ sulbactam	teicoplanin (1)	24 g	4 gr q 6 h	5 weeks	1/1 cured	NA
Stengel et al, Germany-Austria, 2005 [36]	prospective	52	mean 63 years	adult	diabetic foot osteomyelitis-limb-threatening	*S. aureus* (24), *Streptococcus spp.* (14), *Proteus spp.* (13), *Enterococcus spp.* (7), *Pseudomonas spp.* (4), *E. coli* (3), *Citrobacter freundii* (3), Others 4 (1 case of *Klebsiella, Bacteroides, Enterobacter*, and *Serratia spp.* each)	second-line. Twenty-two participants had unsuccessfully been pretreated with different antibiotic drugs for an average of two weeks. Most often used agents were clindamycin, ciprofloxacin, and amoxicillin (in fixed combination with a beta-lactamase inhibitor).	meropenem (14) amoxicillin + clavulanic acid (12) clindamycin (10) ciprofloxacin (10) ceftriaxone (4) imipenem (2) others (5)	8 to 24 g (mean daily dose 14.9 ± 4.9 g)	NA	14.4 + 8.3 days, (3–40 days)	affected limbs could be salvaged in 48 of 52 patients (92.3%)- 4 major amputations	mild nausea and rash (4)
Luengo et al, Spain, 2018 [42]	case report	1	79	adult	total femoral replacement infection	*S. epidermidis*	second-line plus multiple surgeries	daptomycin (1)	8 g	2 gr x 4/d	42 days	1/1 wound healed succesfully	none

(*Continued*)

Table 1. (Continued).

Author, country, year [ref]	Type of study	No. of patients (n) that received intravenous fosfomycin	Age	Pediatric/ Adult	Indication (s)	Isolated pathogens (numbe of patients)	Fosfomycin as first-/second-line line treatment	Antibiotics given with fosfomycin (number of patients)	Fosfomycin daily dose	Fosfomycin dosage regimen	Duration of fosfomycin treatment	Clincal outcome	Adverse events (number of patients)
Gillard et al, France, 2005 [41]	retrospective	3	mean 57.6 years	adult	pyogenic discitis	negative cultures before treatment	first-line followed by other oral treatment combination	fluoroquinolone (2) third generation cephalosporin (1)	NA	NA	mean 18.3 days of IV fosfomycin (then other antibiotic oral treatment for 2–2.5 months in total)	3/3 cured	NA
Baron et al, France, 1986 [37]	retrospective	20	NA	NA	acute osteomyelitis (n = 12), osteoarthritis (n = 8)	*Staphylococcus spp*. (20)	first-line	oxacillin (17), pefloxacin (2), aminoglycoside (1)	200 mg/kg	q 6 or 8 h	NA	10/20 cured, 9 improved, needed surgical interventions, 1/20 failed-amputation	NA
Stockl et al, Germany/ Austria, 2005 [38]	prospective	40	14–80 years (median 60 years)	NA	spondylodiscitis (vertebral osteomyelitis)	*S. aureus* (21) *Streptococcus spp* (3) *E. coli* (3) *S. epidermidis* (2) *Salmonella* (1) *Enterococcus spp*. (1)	56% second line treatment	second generation cephalosporins (22) beta-lactams (5) clindamycin (7) rifampicin (6) vancomycin (3) metronidazole (1)	8–24 g	4 g q 12 h (n = 19) 4 g q 8 h (n = 4) 8 g q 12 h (n = 11) 8 g q 8 h (n = 5)	3–89 days (mean 24 days)	30/40 cured 5/40 improved-needed surgical interventions 5/40 failure	flush (1) taste disorder (1)
Baron et al, France, 2019 [40]	case report	1	43 years	adult	septic pseudoarthrosis	Carbapenemase-producing *Klebsiella pneumoniae*	NA	colistin IV, doxycycline PO	12 g	4 g q 8 h	3 months	cured	none
Narayanasamy et al, Australia 2020 [43]	case report	1	75 years	adult	internal fixation infection	carbapenemase-producing extensively drug-resistant *Pseudomonas aeruginosa*	second-line	colistin	3 g PO for 3 days and 16 g IV	4 g q 6 h	82 days	cured	renal impairment due to colistin

Abbreviations: IV: intravenous, IM: intramuscular, PO: per os, MRSA: methicillin resistant *Staphylococcus aureus*, MSSA: methicillin susceptible *Staphylococcus aureus*, MRCNS: methicillin resistant coagulase negative Staphylococcus, KES: Klebsiella-Enterobacter-Serratia, NA: not applicable

in this analysis) were treated with fosfomycin for osteomyelitis (acute or chronic, hematogenous, vertebral, post-traumatic, post-operative or in the presence of diabetic foot infection–limb threatening osteomyelitis). Arthritis, pyogenic discitis, septic pseudoarthrosis, internal fixation infection and periprosthetic joint infections were some of the other indications for which intravenous fosfomycin was administered [5,26–43].

3.3. Pathogens

The pathogens were isolated from blood cultures, synovial fluid or tissue cultures. Not always a pathogen was isolated in the cases studied, whilst, on the other hand, in several cases, the infection was polymicrobial. In the majority of the cases, the isolated pathogen was *Staphylococcus aureus* (n = 142), including MRSA (n = 9). Coagulase-negative Staphyloccocus was another pathogen found frequently (n = 31), including methicillin resistant coagulase-negative Staphyloccocus (n = 10). In 20 more patients the isolated pathogen was *Staphylococcus spp. Streptococcus spp*. grew in 29 cases, while *Pseudomonas aeruginosa* was isolated in 20 cases. Several other pathogens were less frequently isolated, including *Proteus spp*. (n = 16), *Enterococcus spp*. (n = 13) and *E. coli* (n = 12).

3.4. Fosfomycin as first-line treatment

In 167 patients, intravenous fosfomycin was given as a first-line antibiotic treatment whereas in the rest of the cases, it was given as a second-line choice, when other antimicrobial agents have failed to successfully treat the patient. In some cases, data on whether fosfomycin was a first- or second-line treatment was not clear.

3.5. Combination regimens

Fosfomycin was administered in combination with another antibiotic, in 342 out of 365 patients (93.7%). Specifically, intravenous fosfomycin was combined with cefotaxime in 44 cases [27,28,34,39]. Thirteen patients received fosfomycin with another third-generation cephalosporin [5,36]. Thirty-eight patients received fosfomycin in combination with cefamandole [29] and 22 patients received intravenous fosfomycin in combination with another second-generation cephalosporin [38].

Fosfomycin was given in combination with flucloxacillin in 38 [26], carbapenem in 24 [5,36], clindamycin in 19 [26,36,38], oxacillin in 17 [37], fluoroquinolone in 16 [5,36,41], amoxicillin-clavulanic acid in 16 [26,36], penicillin in 11 [35], glycopeptide in 10 [5], rifampicin in 9 [5,38] and amoxicillin in 2 patients [26], while several other combination choices were less frequently used.

3.6. Fosfomycin dosage and duration of treatment

The dosage of intravenous fosfomycin ranged widely in the cases presented in these studies. It was administered in adult patients in a standard dose of 12 to 16 g/day, ranging from 4 g/day (in one case) to 24 g/day. In some cases, the dose of fosfomycin, mostly when administered in children, was calculated based on body weight, ranging from 50 mg/kg/day to 250 mg/kg/day. Specifically, fosfomycin was dosed as 50 mg/kg/day in two newborns, and in 10 more patients both, adults and children, 100 mg/kg/day (in 15 children), 200 mg/kg/day (in 82 children and 20 more patients including adults and children) and 250 mg/kg/day (in 36 children).

The duration of treatment with fosfomycin was also variable, with a maximum duration of three months. In some cases, the intravenous treatment of the patients was followed by oral antibiotics [26,27,31,41].

3.7. Clinical outcomes

Three hundred out of the 365 patients (82.2%) who received intravenous fosfomycin, alone or in combination with another antibiotic, for the treatment of bone and joint infections, were succesfully treated. Fourteen patients improved but needed further surgical intervention [37,38]. In Fifteen patients, osteomyelitis relapsed [32,34,35], 15 patients were lost on follow-up [5,32]. Six patients were considered failure of treatment [37,38]. Three patients with wrist osteomyelitis had radiological abnormalities of the wrist after treatment. One of them, complained of moderate pain and limitation of forearm pronation/supination, in the 7 year follow-up visit [27]. In one prospective study, one patient died early during hospitalization and in 4 patients the outcome was considered unfavorable – due to death associated with sepsis [5]. In cases with diabetic foot osteomyelitis, 4 out of 52 patients with a high risk of major amputation and failure of previous antibiotic treatment had major amputations but the remaining 48 patients had their infected limbs salvaged [36]. There is missing data on the clinical outcome of two patients in one study [29].

3.8. Adverse events

Data on side effects of fosfomycin in the available data is scarce. Mild gastrointestinal disorders were reported in 10 patients, exanthema in 12 patients [26,32,36], while leukopenia and neutropenia were identified in one and three patients, respectively, [26,34]. Hypernatremia in two cases and increase of ALT in another case were also reported. Flush was reported in one patient and taste disorder in another one [38]. Given that fosfomycin was administered in combination with other antibiotics, it cannot be clarified which agent was responsible for these side effects [34].

4. Evaluation of the published evidence

The use of intravenous fosfomycin for the treatment of bone and joint infections was successful in 82.2% of the cases included in this analysis. This high rate of effectiveness suggests that fosfomycin may be beneficial when treating patients with bone and joint infections. According to the European Medicines Agency (EMA) [44], bone and joint infections are one of fosfomycin's approved therapeutic indications [45]. As shown in the data presented in this analysis,

osteomyelitis was the main indication for which fosfomycin was administered (81.1% of the total patients), but ranging from mild to moderate cases like those with hematogenous origin to those infections that are intrinsically considered difficult-to-treat and at high risk of relapse or therapeutic failure, like chronic osteomyelitis or diabetic foot infections. The rest of the patients received fosfomycin for arthritis, periprosthetic joint infections or pyogenic discitis, septic pseudoarthrosis, and internal fixation infection with excellent clinical outcomes as well.

A considerable proportion of the data included in this evaluation are from pediatric patients. This is due, at least in part, to the fact that hematogenous osteomyelitis is a common infection in children. The increased blood supply to the bone metaphysis in children is the major pathophysiological reason why bone and joint infections are often seen in young ages. There are data supporting that 50% of childhood osteomyelitis present in the age of <5 years [46]. Fosfomycin may be administered in children of all age groups, including premature neonates.

However, more recent data indicate a shift in clinical practice toward the consideration of use of intravenous fosfomycin in adult patients with complicated cases of osteomyelitis, e.g. those with failure of initial antibiotic therapy, diabetic foot infections, chronic osteomyelitis, infections with abscess formation or infected foreign bodies, particularly difficult-to-reach infections (e.g. discitis), or infections with involvement of multidrug-resistant pathogens or polymicrobial infections [5,33,36,38,40,43,47–49]. This observation is also in line with current treatment algorithms where fosfomycin is recommended for the combination therapy of periprosthetic joint infections or infections after fracture fixation [50–52].

Independently of age, the most common pathogen in bone and joint infections, is *Staphylococcus aureus*, which is in accordance with the findings of this analysis [53]. In foreign bodies associated with infections, coagulase-negative staphylococci are commonly involved. Several other organisms are also isolated in osteomyelitis, especially in immunocompromised patients (e.g. HIV, diabetes) [54]. The data resulting from this analysis are in accordance with the already published information [54], as, apart from *Staphylococcus*, that was the major isolated pathogen, other microorganisms, such as Streptococci, Enterobacteriaceae, Enterococci, and *Pseudomonas aeruginosa* were also isolated [54].

The administration of intravenous fosfomycin in the vast majority of the cases presented in this analysis (93.7%) was part of a combination regimen. Common partners of fosfomycin were second and third-generation cephalosporins, penicillin derivatives, carbapenems, clindamycin, fluoroquinolones and glycopeptides. In general, the recommended treatment for bone and joint infections is a long course of intravenous antibiotics, either as monotherapy or in combination. Combination of antibiotics is usually a choice for the treatment of chronic osteomyelitis, complicated infections and prosthetic joint infections. The synergistic effect achieved when antibiotics are given in combination, together with the possibility of decrease of the emergence of resistance (especially with infections with high microbial load as suggested by the effect of high inoculum in vitro studies) [55,56] are the main reasons why fosfomycin is administered in combination regimens. In a recent review, data suggest that the pooled estimate for resistance development during fosfomycin monotherapy was 3.4% and therefore comparable with beta-lactam antibiotics [57]. Another aspect that speaks in favor of a fosfomycin-containing combination therapy is its excellent penetration into the bone tissue, as standard antibiotics like flucloxacillin in case of *S. aureus* involvement show particular poor bone penetration [58]. As far as it concerns the dosage of fosfomycin, in the cases presented in this analysis, it ranged between 4 g/day (in only one case) and 24 g/day. However, fosfomycin dosages below 12 g/day might be associated with a higher risk of treatment failure [38]. According to the SPC of the medication, the recommended dose for the treatment of osteomyelitis is 12–24 g/day with the note that high doses should be used in severe infections with less susceptible bacteria and with caution because there are limited safety data for doses of more than 16 g/day [44]. In the pediatric population, fosfomycin was dosed based on age and body weight. The dose regimen ranged from 50 mg/kg/day to 250 mg/kg/day.

The duration of treatment was also variable. Data presented in this paper include patients that received intravenous fosfomycin for as little as 5 days, as well as patients who were treated with fosfomycin for almost 90 days. In many cases, the intravenous treatment was completed by oral administration of antibiotics.

Intravenous fosfomycin was well tolerated. Only in seven studies, there are data about the occurrence of side effects. Mild gastrointestinal discomfort, like diarrhea or nausea, was reported in ten patients. Hematological side effects (neutropenia, and leukopenia) were rare, as they presented in only three patients. Allergic exanthema was reported in 12 patients. Flash and taste disorder were reported in one case each. A causal relationship between these adverse effects and fosfomycin cannot be established, because the antibiotic was given in combination with other agents.

In the evaluation and interpretation of the data presented in this article, several limitations should be taken into consideration. First, data derive from four case series, five case reports, one case control study, three retrospective, and six prospective studies. It is not a rich database, even though the number of patients treated with intravenous fosfomycin was considerable. Second, the information provided comes from a heterogenous sample of patients. The different age of the patients, various dosage and duration of treatment with fosfomycin, and the different definition of clinical success in each study, make a direct comparison of the results, more difficult. Also, one should take into consideration the publication bias in which the published case reports and case series, usually represent successful cases and not failures of treatment, thus creating a result that overestimates the effectiveness of the studied medication.

5. Expert opinion

The fact that the use of intravenous fosfomycin, especially when used in combination with other antibiotics, resulted in

clinically successful treatment in 82.2% of the patients studied in this analysis, allows for serious consideration of fosfomycin for the treatment of bone and joint infections. The unique mode of action of fosfomycin, its low toxicity, the wide spectrum of bactericidal activity, and its high penetration into deep-seated infections, make fosfomycin an attractive choice for the treatment of bone and joint infections.

Bone and joint infections are serious infections affecting patients of all ages, from neonates to elderly people and are a major cause of disability, morbidity and mortality. The difficult-to-reach osseous tissue, together with the fact that multidrug-resistant bacteria are oftentimes involved in these cases, increase the demand for a wide range of antibiotic treatment options. Fosfomycin thus, may be considered as an effective agent in combination with other antibiotics for the treatment of bone and joint infections, caused by *Staphylococcus aureus*, including MRSA, coagulase-negative Staphylococci, Enterococci, *Streptococcus spp, Enterobacteriaceae*, and *Pseudomonas aeruginosa*.

Successful management of bone and joint infections requires an interdisciplinary treatment strategy to eradicate the infection, thus avoiding persistence and relapse in order to achieve a favorable outcome. However, randomized clinical studies comparing different orthopedic techniques, antimicrobial agents, or treatment durations are mostly missing. Therefore, learning from the clinical experience is particularly important [59]. As shown in this analysis, there is considerable available evidence from several published papers that support the consideration of intravenous fosfomycin for the treatment of patients with bone and joint infections. Also, there are several ongoing prospective studies on intravenous fosfomycin for the treatment of patients with bone and joint infections [60,61]. Based on the available data, intravenous fosfomycin may be beneficial for empiric and targeted first-line treatment [62], but also offers a reasonable therapeutic option when the infection fails to respond to initial antibiotic therapy or concurrent presence of difficult-to-treat pathogens. Future research could help to further optimize the combination therapy with intravenous fosfomycin for the treatment of patients with bone and joint infections.

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Abbreviations

ALT: alanine aminotransferase
AUC: area under the curve
EMA: European medicines agency
ESBL: extended-spectrum beta-lactamase-producing
MDR: multidrug resistant
MRSA: methicillin-resistant *Staphylococcus aureus*
PAE: postantibiotic effect
SPC: summary of product characteristics
XDR: extensively drug resistant

Notes on contribution

All authors have substantially contributed to the production of the article and agreed with its final version.

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