International Journal of Infectious Diseases 15 (2011) e732–e739

Contents lists available at SciVerse ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Review

The revival of fosfomycin

Argyris S. Michalopoulos *, Ioannis G. Livaditis, Vassilios Gougoutas

Intensive Care Unit, Henry Dunant Hospital, 107 Mesogeion Ave, 11526 Athens, Greece

ARTICLE INFO

Article history:
Received 12 January 2011
Received in revised form 30 June 2011
Accepted 11 July 2011

Corresponding Editor: J. Peter Donnelly, Nijmegen, the Netherlands

Keywords:
Enterococcus faecalis
Escherichia coli
Klebsiella pneumoniae
Pseudomonas aeruginosa
Urinary tract infections
Nosocomial infections

SUMMARY

Fosfomycin, originally named phosphonomycin, was discovered in Spain in 1969. There are three forms of fosfomycin: fosfomycin tromethamine (a soluble salt) and fosfomycin calcium for oral use, and fosfomycin disodium for intravenous use. Fosfomycin is a bactericidal antibiotic that interferes with cell wall synthesis in both Gram-positive and Gram-negative bacteria by inhibiting the initial step involving phosphoenolpyruvate synthetase. It has a broad spectrum of activity against a wide range of Gram-positive and Gram-negative bacteria. It is highly active against Gram-positive pathogens such as *Staphylococcus aureus* and Enterococcus, and against Gram-negative bacteria such as *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. Its unique mechanism of action may provide a synergistic effect to other classes of antibiotics including beta-lactams, aminoglycosides, and fluoroquinolones. Oral fosfomycin is mainly used in the treatment of urinary tract infections, particularly those caused by *Escherichia coli* and *Enterococcus faecalis*. Intravenous fosfomycin has been administered in combination with other antibiotics for the treatment of nosocomial infections due to multidrug-resistant (MDR) Gram-positive and Gram-negative bacteria. Fosfomycin has good distribution into tissues, achieving clinically relevant concentrations in serum, kidneys, bladder wall, prostate, lungs, inflamed tissues, bone, cerebrospinal fluid, abscess fluid, and heart valves. Fosfomycin is well tolerated, with a low incidence of adverse events. Further randomized controlled trials are needed in order to evaluate the efficacy of intravenous fosfomycin for the management of nosocomial infections due to MDR pathogens.

1. Introduction

Fosfomycin, originally named phosphonomycin, was discovered in Spain in 1969.[1] It is a phosphonic acid derivative, with an extremely low molecular weight, and shows almost no binding to proteins. Fosfomycin is a unique antibiotic that is chemically unrelated to any other known antibacterial agent. Its empirical formula is $C_3H_7O_4P{\cdot}C_4H_{11}NO_3$ and its chemical structure is shown in Figure 1.

2. Forms of fosfomycin

Fosfomycin is available in two oral formulations – fosfomycin tromethamine (synonym trometamol), a soluble salt with improved bioavailability over fosfomycin, which is synthetically prepared, and fosfomycin calcium. Fosfomycin tromethamine is the preferred formulation for oral administration of fosfomycin because it is more readily absorbed into the blood compared to fosfomycin calcium.[2,3] There is also an intravenous formulation – fosfomycin disodium.

3. Mechanism of action

Fosfomycin is a bactericidal antibiotic that interferes with cell wall synthesis in both Gram-positive and Gram-negative bacteria by inhibiting the initial step involving phosphoenolpyruvate synthetase. Fosfomycin enters the cells of fosfomycin-susceptible bacteria by means of two different transport uptake systems: a constitutively functional L-α-glycerophosphate transport system (GlpT) and the hexose–phosphate uptake system (UhpT).[4] It inhibits the synthesis of peptidoglycan by blocking the formation of *N*-acetylmuramic acid.[5]

Fosfomycin has a broad spectrum of activity against a wide range of Gram-positive and Gram-negative bacteria. Its unique mechanism of action may provide a synergistic effect to other antibiotics including beta-lactams, aminoglycosides, and fluoroquinolones.[6–8]

4. Pharmacokinetics and pharmacodynamics

Fosfomycin is rapidly absorbed following oral administration and is converted to the free acid, fosfomycin. Bioavailability is around 40% for fosfomycin tromethamine vs. 12% for the calcium salt of fosfomycin; 30–60% of fosfomycin tromethamine is excreted unchanged in the urine vs. 9–18% for the calcium salt

* Corresponding author. Tel.: +30 210 6972353; fax: +30 210 6972354.
E-mail address: amichalopoulos@hol.gr (A.S. Michalopoulos).

1201-9712/$36.00 – see front matter © 2011 International Society for Infectious Diseases. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.ijid.2011.07.007

of fosfomycin.[9] Fosfomycin has a renal elimination of 95%. No tubular secretion occurs. Fosfomycin has a relatively long elimination half-life, which varies between 4 and 8 h.[10] In patients with chronic renal failure, the half-life of fosfomycin is increased significantly (up to 50 h) and is associated with a lower fosfomycin recovery in urine.

Fosfomycin has good distribution into tissues, achieving clinically relevant concentrations in serum, kidneys, bladder wall, prostate, lungs, inflamed tissues, bone, cerebrospinal fluid, abscess fluid, and heart valves.[11–14] Frossard et al.[15] demonstrated high fosfomycin concentrations in plasma and soft tissues, suggesting a high degree of tissue penetration. Sauermann et al.[16] evaluated fosfomycin penetration into suppurative lesions to determine whether it was reaching sufficient concentrations to eradicate clinically relevant bacteria in abscess fluid. They found that there was a high inter-individual variability in the pharmacokinetics of fosfomycin in pus due to highly variable abscess permeability. They concluded that in many patients, fosfomycin concentration in abscess fluid would be expected to exceed the minimum inhibitory concentrations ($MIC_{50/90}$s) of several relevant bacteria after multiple doses.

Although fosfomycin crosses maximally into cerebrospinal fluid (CSF) in the presence of inflamed meninges,[17] the activity of fosfomycin against Gram-positive and Gram-negative bacteria is notably reduced in human CSF.[18] Fosfomycin penetrates sufficiently into various tissues and CSF.[19] Pfausler et al.[20] found that 8 g of fosfomycin three times a day provides sufficient antimicrobial concentrations in the CSF in ventriculitis caused by susceptible pathogens.

5. Susceptibility testing

The agar dilution, broth dilution, and disk diffusion methods are used in order to determine the in vitro susceptibility of Gram-positive and Gram-negative bacteria to fosfomycin.[21] Agar or broth dilution testing using Mueller–Hinton agar or broth, respectively, supplemented with 25 μg/ml glucose-6-phosphate in an aerobic atmosphere at 35–37 °C is generally recommended.[9] However, it should be noted that some authorities suggest that broth dilution testing should not be performed to test susceptibility to fosfomycin.[22]

In a study by de Cueto et al., the agar dilution, broth microdilution, and disk diffusion methods were compared to determine the in vitro susceptibility of 428 extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* and *Klebsiella pneumoniae* to fosfomycin. Fosfomycin showed high activity against all ESBL-producing strains. Excellent agreement between the three susceptibility methods was found for *E. coli*, whereas marked discrepancies were observed for *K. pneumoniae*.[23]

Diffusion techniques requiring measurement of zone diameters provide reproducible estimates of the susceptibility of bacteria to fosfomycin. Results of the standard single-disk susceptibility tests with disks containing 200 μg of fosfomycin and 50 μg of glucose-6-phosphate should be interpreted according to the following criteria: zone diameter ≥16 mm means a susceptible strain; zone diameter 13–15 mm means an intermediate strain; and zone diameter ≤12 mm means a resistant strain.

The MIC values should be interpreted according to the following criteria: MIC ≤64 μg/ml: susceptible (S); MIC 128 μg/ml: intermediate (I); MIC ≥256 μg/ml: resistant (R).

6. Antimicrobial activity

The antimicrobial activity of fosfomycin is broad. Fosfomycin shows an excellent bactericidal activity against Gram-positive cocci, such as methicillin-sensitive *Staphylococcus aureus* (MSSA), cephalosporin- and penicillin-resistant *Streptococcus pneumoniae*,[24,25] methicillin-resistant *S. aureus* (MRSA),[26] and *Enterococcus* species, even in vancomycin-resistant strains.[27] Fosfomycin also shows very good activity against many Gram-negative bacteria, such as *E. coli*, *Proteus mirabilis*, *K. pneumoniae*, *Enterobacter* species, *Citrobacter spp*, *Serratia marcescens*, *Neisseria meningitidis*, *Shigella spp*, and *Salmonella typhi*, which are generally inhibited at fosfomycin concentrations of ≤64 μg/ml. In contrast, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* are usually resistant to fosfomycin.[28–30] The high MIC of fosfomycin against *A. baumannii* and *P. aeruginosa* implies the clinical ineffectiveness of fosfomycin alone. However, fosfomycin may be effective in combination with other antibiotics, such as beta-lactam antibiotics (cefepime, aztreonam, or meropenem) or aminoglycosides.[7,8,31–33] It should be noted that although *Bacteroides fragilis* is resistant to fosfomycin, *Peptococcus niger* and *Peptostreptococcus spp* are usually fosfomycin-sensitive. However, fosfomycin is less active than penicillin, cephalothin, clindamycin, and lincomycin against these cocci.[34]

Falagas et al.[35] systematically reviewed 17 studies (accounting for 5057 clinical isolates of *Enterobacteriaceae*) evaluating the antimicrobial activity and clinical effectiveness of fosfomycin for infections caused by multidrug-resistant (MDR) *Enterobacteriaceae*, including ESBL. Eleven studies reported that at least 90% of the isolates were susceptible to fosfomycin. Using a provisional MIC susceptibility breakpoint of 64 mg/l or less, the majority of *E. coli* and *K. pneumoniae* isolates producing ESBL were susceptible to fosfomycin (96.8% and 81.3%, respectively). In two clinical studies, oral treatment with fosfomycin tromethamine was clinically effective against complicated and uncomplicated lower urinary tract infections (UTIs) caused by ESBL-producing *E. coli* in the majority of patients. Susceptibility of ESBL-producing *K. pneumoniae* to fosfomycin has also been observed in previous studies.[36,37] In addition, the in vitro activity of fosfomycin against blaKPC-containing *K. pneumoniae*, including those non-susceptible to tigecycline or colistin, has been examined by Endimiani et al.[38]

Samonis et al.[39] examined the sensitivity of 594 non-urinary Gram-negative bacteria. In total, 385 (64.8%) were susceptible to fosfomycin. Specifically, all *E. coli*, *Proteus mirabilis*, and *Salmonella* species isolates were susceptible. In addition, *K. pneumoniae* (including carbapenem-resistant strains), *Enterobacter* species, and *P. aeruginosa* isolates were susceptible to fosfomycin (77.7%, 68.8%, and 64.5%, respectively). Susceptibility was highest amongst isolates taken from outpatients (73.8%) and lowest for intensive care unit (ICU) isolates (48.4%). Isolates originating from the pediatric wards exhibited higher susceptibility (71.4%) than isolates originating from other departments (64%).

Data from the same hospital dealing with fosfomycin antimicrobial activity against Gram-positive non-urinary isolates showed that 1275 isolates (69.1%) were susceptible to fosfomycin. Specifically, *S. aureus* including MRSA (99.3%) and coagulase-negative staphylococci (77.5%) were susceptible to fosfomycin. Among 42 *S. pneumoniae*, 64 *Streptococcus pyogenes*, and 93 other streptococcal isolates, 61.9%, 40.6%, and 48.4%, respectively, were susceptible to fosfomycin. Fosfomycin was inactive against the 166 enterococcal isolates tested.[21]

Fosfomycin exerts time-dependent killing against Gram-positive and Gram-negative bacteria. Bacteria that adhere to foreign materials, medical devices, implant surfaces, and damaged tissues can encase themselves in a self-made polymeric matrix of polysaccharide and protein, forming biofilms. Biofilms play a significant role in the development and persistence of several nosocomial infections such as central venous catheter-related infections and urinary catheter-related UTIs. In biofilms, resistance to antimicrobials is increased. Biofilms facilitate the spread of antibiotic resistance by promoting horizontal gene transfer.

Antibiotic resistance of bacteria in the biofilms and the stability of biofilms are major contributors to the chronicity of nosocomial infections. Bacterial biofilms are difficult to detect in routine diagnostics and are inherently tolerant to host defenses and several classes of antibiotics. Fosfomycin has shown antimicrobial activity against biofilms, particularly in combination with fluoroquinolones or aminoglycosides.[40–43] Based on reports, fosfomycin can break up biofilms to enhance the permeability of other antibiotics.[44]

7. Mechanism of fosfomycin resistance

Bacterial resistance to fosfomycin is exerted by three mechanisms – two of them are located on the chromosome and the third is of plasmid origin.[45] Bacterial resistance to fosfomycin may be attributed to a genetic mutation in one or both of the chromosomally encoded transport systems GlpT and/or UhpT, and less commonly by a fosfomycin-modifying enzyme leading to products associated with no antibacterial activity.[46,47]

Plasmid-encoded fosfomycin resistance is exerted by a gene located in a transposon; it encodes a 16-kilodalton protein located in the cytoplasm and also encodes constitutive synthesis.[48] Plasmid-encoded fosfomycin resistance is due to modification of the antibiotic molecule by an enzyme called metalloglutathione transferase, a glutathione S-transferase that catalyzes the formation of a covalent bond between the sulfhydryl residue of the cysteine in glutathione and C-1 of fosfomycin.[49,50] Four fosfomycin-modifying enzymes have already been described. These enzymes catalyze the formation of a glutathione–fosfomycin (FosA), L-cysteine–fosfomycin (FosB), ATP–fosfomycin (FosC), and water–fosfomycin (FosX) adducts.[51] FosA is a Mn(II)- and K^+-dependent glutathione transferase.[52] FosB is a Mg^{2+}-dependent L-cysteine thiol transferase. FosX is a Mn(II)-dependent fosfomycin-specific epoxide hydrolase.[53] The metalloglutathione transferase FosA catalyzes the conjugation of glutathione to C-1 of fosfomycin, rendering it ineffective as an antibacterial agent.[46] The plasmid-mediated fosfomycin glutathione S-transferase genes *fosA* and *fosB* have been found in a low percentage of isolated strains.[54]

The development of cross-resistance to fosfomycin by the use of other classes of antibacterial agents such as beta-lactams and aminoglycosides has not been regarded as significant, probably due to the unique target of action of fosfomycin.[55]

8. Clinical use

8.1. Oral fosfomycin in UTIs

Fosfomycin is mainly used in the treatment of UTIs, particularly those caused by *E. coli* and *Enterococcus faecalis*, and in combination with other antibiotics in the treatment of nosocomial infections due to resistant Gram-positive and Gram-negative bacteria.[41,55–57] In most European countries, oral fosfomycin has been used for many years, mainly in the treatment of uncomplicated cystitis or other UTIs, particularly those caused by *E. coli* and *E. faecalis*. In the USA, the Food and Drug Administration has approved oral fosfomycin only for uncomplicated UTIs.

Rudenko and Dorofeyev[58] examined 317 non-pregnant females suffering from recurrent lower UTIs (at least three episodes in the preceding 12 months) in order to assess the efficacy and safety of fosfomycin tromethamine in the prevention of infectious recurrences of lower UTIs. One hundred and sixty-six patients were randomized to receive fosfomycin treatment and 151 to receive placebo treatment. Patients received 3 g fosfomycin or placebo every 10 days for 6 months. Thereafter they were followed up for another 6 consecutive months. They found 0.14 infections per patient per year in the fosfomycin group and 2.97 infections per patient per year in the placebo group ($p < 0.001$). The time to first infection recurrence was significantly longer in the fosfomycin group (38 days) than in the placebo group (6 days) ($p < 0.01$). The number of patients with at least one episode of recurrent infection and the number of episodes per patient during treatment as well as during the follow-up period were significantly lower in the fosfomycin group than in the placebo group.

Falagas et al.[59] reported the results of their meta-analysis of 27 randomized controlled trials (RCTs) dealing with the effectiveness and safety of fosfomycin for the treatment of cystitis in pregnant and non-pregnant women. Twenty-seven trials (eight double-blind) were included. Sixteen of these trials involved exclusively non-pregnant female patients and five involved pregnant patients. Regarding clinical success, no difference was found in the comprehensive analysis regarding all comparators combined in trials involving non-pregnant females, while insufficient relevant data were provided from trials involving pregnant patients. No difference between fosfomycin and comparators was also found in all comparisons regarding the remaining effectiveness outcomes, namely microbiological success/relapse/re-infection. Fosfomycin had a comparable safety profile to the evaluated comparators in non-pregnant women, whereas it was associated with significantly fewer adverse events in pregnant women.

Pullukcu et al.[60] examined the effect of fosfomycin tromethamine in the treatment of ESBL-producing *E. coli*-related lower UTI in 52 adult patients receiving 3 g per day fosfomycin tromethamine, three times. Overall clinical success was 94.3% and microbiological success was 78.5%. Similar good results have been reported from a recent Spanish clinical study.[61]

A single dose of fosfomycin tromethamine is well absorbed and produces a therapeutic concentration in the urine for 1–3 days. Comparative clinical trials suggest that a single 3-g dose of fosfomycin tromethamine is as clinically effective as 7- to 10-day treatment regimens of standard agents such as nitrofurantoin, norfloxacin, and trimethoprim/sulfamethoxazole used to treat UTIs. Fosfomycin tromethamine is well tolerated and appears safe for use during pregnancy.[62] According to Schito, fosfomycin tromethamine remains a reliable therapeutic option for uncomplicated UTI due to its main advantages, including single dose usage and very high and sustained urinary concentrations that rapidly kill bacteria, reducing the opportunity for mutant selection. In addition there is no animal feed that contains the drug, resistance is most commonly acquired by chromosomal mutations that do not spread easily, and the biological cost of these genetic modifications is high. In addition, fosfomycin tromethamine has excellent tolerability and safety.[63]

8.2. Intravenous fosfomycin in clinical use

Regarding the intravenous administration of fosfomycin, Falagas et al.[2] studied 1604 patients with Gram-positive and Gram-negative infections (including pneumonia, osteomyelitis, meningitis, surgical infections, obstetric and gynecological infections, arthritis, sepsis, peritonitis, cervical lymphadenitis, ear, nose, and throat infections, eye infections, diabetic foot infections, and typhoid fever). Patients were treated with intravenous fosfomycin alone or in combination with other antibiotics. Cure was achieved in 81.1% of patients and improvement in approximately 3%.

Recently, intravenous fosfomycin has been administered in critically ill patients with sepsis or nosocomial-acquired infections due to MRSA, vancomycin-resistant Enterococcus, and MDR Gram-negative bacteria, especially carbapenem-resistant *K. pneumoniae*, in combination with other antibiotics, due to its unique mechanism of action and its protective effect against nephrotoxicity induced by aminoglycosides or colistin.[64–66] Michalopoulos et al.[65] examined the effectiveness and safety of fosfomycin in critically ill

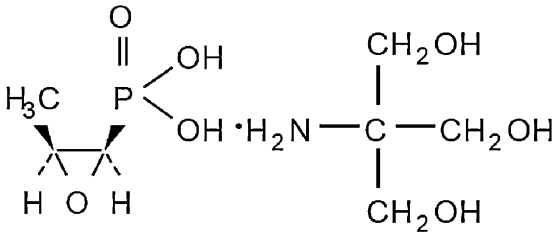

Figure 1. Chemical structure of fosfomycin.

patients suffering from ICU-acquired infections due to carbapenem-resistant *K. pneumoniae*. They concluded that fosfomycin may be considered an alternative for the treatment of infections due to carbapenem-resistant *K. pneumoniae* in adult patients, especially in combination with other antibiotics. Data also suggest that the intravenous formulation of fosfomycin could be useful for eye infections.[67]

One rationale for combining fosfomycin with a second antimicrobial agent is to prevent the emergence of fosfomycin-resistant strains. Fosfomycin has regained attention because of its in vitro activity against ESBL-producing *Enterobacteriaceae* and MDR *P. aeruginosa*. Clinical studies dealing with the intravenous administration of fosfomycin for curative use in adult patients are listed in Table 1. It should be noted that the clinical utility of fosfomycin in nosocomial infections due to MDR Gram-negative bacteria should be explored further in future RCTs.

Fosfomycin is approved in several European countries for the therapy of soft-tissue infections and sepsis.[68] However, it should be noted that the intravenous formulation of fosfomycin is available in five countries in Europe – Spain, France, Germany, Austria, and Greece.

All studies dealing with the curative use of intravenous fosfomycin in adult patients are presented in Table 1.[33,65,66,69–84]

8.3. Fosfomycin for surgical prophylaxis

Ishizaka et al.[85] compared the efficacy of fosfomycin (2 g/dose) and cefotiam (1 g/dose), both administered intravenously 30 min before surgery, for preventing postoperative infections in patients undergoing urological surgery. Both antibiotics were administered twice daily for 3 days after surgery. The reduction in the rate of surgical site infections was 90.8% overall – 90.5% for fosfomycin and 91.0% for cefotiam. Fosfomycin and cefotiam response rates were 92.9% and 94.9%, respectively, in transurethral surgery patients, and 87.2% and 85.4%, respectively, in patients undergoing open-surgery (consisting of clean surgery, clean-contaminated surgery, and contaminated surgery). The surgical-site infection rates in open surgery were 0% for fosfomycin and 4.9% for cefotiam. However, no statistically significant difference was found.

In comparative peri-operative prophylaxis trials that included 1212 patients (mainly undergoing colorectal surgery), the fosfomycin–metronidazole combination led to results similar to those achieved with the combination of other antibiotics, such as doxycycline, ampicillin, or cephalothin and metronidazole. The authors concluded that fosfomycin might be considered as an alternative agent for infections caused by sensitive Gram-positive and Gram-negative bacteria, in addition to its traditional use in treating uncomplicated urinary tract and gastrointestinal infections.[2]Clinical studies dealing with the intravenous administration of fosfomycin for surgical prophylaxis in adult patients are shown in Table 2.[85–91]

9. Dosing

9.1. Oral fosfomycin

The usual oral dose of fosfomycin calcium is the equivalent of 0.5–1 g of fosfomycin administered every 6–8 h. Higher doses should be given parenterally. For uncomplicated cystitis, a single dose of fosfomycin (3 g) is adequate. For complicated cystitis, a single dose of fosfomycin (3 g) administered every 2–3 days is necessary. In total, three doses of fosfomycin are needed. In the case of oral administration, no dosage adjustment is necessary in patients with hepatic or renal failure.

9.2. Intravenous fosfomycin

Several regimens of intravenous fosfomycin are used worldwide. Fosfomycin disodium is given intravenously and on rare occasions intramuscularly. The daily dose ranges from 12 to 16 g on average, administered in 2–4 infusions. Daily doses of up to 20 g

Table 1
Studies dealing with the curative use of fosfomycin in adult patients (intravenous administration)

Study	Patients (*n*)	Age, mean years	Pathogens	Infection	Combination therapy	Mortality (%)
Alvarez et al.[71]	1	-	*Serratia marcescens*	Endophthalmitis	Ceftriaxone + amikacin	0
Boulard et al.[72]	4	-	*Staphylococcus epidermidis*	CSF shunt infection	Aminoglycoside	0
Bureau-Chalot et al.[73]	1	-	*Stomatococcus mucilaginosus*	Spondylodiscitis	Cefotaxime	0
Florent et al.[70]	72	55	Multiple	Multiple	Multiple	13
Gillard et al.[74]	8	-	-	Pyogenic discitis	Quinolone[a]	0
Guerin et al.[75]	1	46	*Pseudomonas aeruginosa*	Prostatitis	Aztreonam	0
May et al.[76]	7	-	Multiple	Meningitis	Ceftriaxone	-
Meissner et al.[69]	60	37.4	Multiple	Chronic osteomyelitis	No combination therapy	26.4
Michalopoulos et al.[65]	11	67.5	MDR *Klebsiella pneumoniae*	ICU-acquired infection	Multiple	18.2
Mirakhur et al.[33]	15	23	*Pseudomonas aeruginosa*	Cystic fibrosis	Multiple	0
Nakayama et al.[77]	1	64	MRSA	Toxic shock syndrome	Vancomycin	0
Nissen et al.[78]	17	-	Multiple	Pneumonia	Ampicillin	6
Ortler et al.[79]	1	35	*Staphylococcus aureus*	Wound infection	Cefmenoxime	0
Portier et al.[80]	16	-	MRSA	Bacteremia; bone/ joint infection/meningitis	Cefotaxime	0
Roualdes et al.[81]	2	-	*Staphylococcus epidermidis*, *Staphylococcus capitis*, *Micrococcus varians*	CSF shunt infection	Vancomycin, rifampin	0
Silbermann et al.[82]	1	17	*Staphylococcus epidermidis*	Meningitis	Vancomycin	0
Ueda et al.[83]	65	-	Multiple	Multiple	0	46.1
Yamaguchi et al.[66]	1	64	MRSA	Pneumonia and sepsis	Arbekacin	0
Zink et al.[84]	1	81	*Staphylococcus albus*	Ventriculoatrial shunt meningitis	Gentamicin	0

[a] Eighteen patients received usually a fluoroquinolone with a beta-lactam or fosfomycin.

Table 2
Studies dealing with intravenous administration of fosfomycin for surgical prophylaxis in adult patients

Study	RCT	Type of surgery	Patients (*n*)	Combination of antibiotics	Post-op infection rate
Andåker et al.[86]	Yes	Elective colorectal	559	Yes (metronidazole)	Abdominal infection (4.6%); remote infection (15.1%)
Andåker et al.[87]	Yes	Emergency abdominal	381	Yes (metronidazole)	Sepsis (1.6%)
Ishizaka et al.[85]	Yes	Urologic	95	No	9.5%
Lebreton et al.[88]	No	Open heart surgery	34	Yes (pefloxacin)	5.9%
Lindhagen et al.[89]	Yes	Colorectal	49	Yes (metronidazole)	Sepsis (0%)
Nøhr et al.[90]	Yes	Elective colorectal	72	Yes (metronidazole)	13%
Shinagawa et al.[91]	No	Upper gastroenterological and hepatobiliary surgery	162	No	13.2%

RCT, randomized controlled trial.

have been given intravenously for the treatment of life-threatening infections. Renal impairment significantly decreases the excretion of fosfomycin. For intravenous administration of fosfomycin, the doses should be reduced if the creatinine clearance is less than 50 ml/min.

10. Contraindications and adverse effects

Hypersensitivity to fosfomycin or any components of its formulation are the main contraindications for its administration.[92]

10.1. Oral fosfomycin

Oral fosfomycin is well tolerated with a low incidence of adverse events. These comprise mainly gastrointestinal symptoms that are transient, mild, and self-limiting,[93] and include diarrhea (10%), nausea (5%), abdominal pain (2%), and dyspepsia (1–2%). Other adverse effects include headache, dizziness, back pain, weakness, vaginitis, rhinitis, and pharyngitis. Significant laboratory alterations reported include an increased eosinophil count, increased or decreased white blood cell count, increased bilirubin, increased alanine aminotransferase, increased aspartate aminotransferase, increased alkaline phosphatase, decreased hematocrit, decreased hemoglobin, and alterations in platelet count. Changes have generally been transient and not clinically significant.

Fosfomycin is not a nephrotoxic agent. Previous studies performed in animals have shown that fosfomycin has a protective effect against nephrotoxicity due to aminoglycosides, by inhibiting aminoglycoside-induced histamine release from mast cell destruction.[94] The prolonged use of oral fosfomycin may result in fungal or bacterial superinfections, including rare *Clostridium difficile*-associated diarrhea and pseudomembranous colitis.[95] It should be noted that the adverse events associated with fosfomycin do not usually necessitate the discontinuation of treatment.

10.2. Intravenous fosfomycin

The intravenous administration of fosfomycin is associated with a low incidence of adverse effects. The most significant adverse effect related to the administration of fosfomycin disodium is a high sodium intake, which could be a limitation in patients with heart or renal failure. It should be emphasized that 1 g of intravenous fosfomycin brings 0.33 g (14.4 mEq) of sodium. Other adverse effects reported rarely are allergic reactions, nausea, neutropenia, hypereosinophilia, and local phlebitis.[33,69] Recently, Florent et al.[70] reported adverse effects associated with intravenous fosfomycin administered in 72 patients. Hypokalemia was the most common (26%), followed by injection-site reaction (pain) seen in 4% and heart failure or hypertension in 3% of patients. However, these adverse effects are usually mild, tolerable, and transient.

11. Drug interactions

Scarce data are available regarding fosfomycin interactions. A total of two drugs are known to interact with fosfomycin: balsalazide, which interacts with the oral formulation of fosfomycin (moderate interaction), and metoclopramide (mild interaction). The latter, when given concomitantly with fosfomycin, may lead to a lower serum concentration and urinary excretion of fosfomycin. The mechanism of action appears to be due to increased gastrointestinal mobility.[96]

12. Synergistic activity

The efficacy of a fosfomycin combination with a second antibiotic against *S. aureus* and *E. faecalis* has been evaluated in vitro and in vivo.[97–101] A number of previous studies have shown that fosfomycin can act synergistically with beta-lactams and with aminoglycosides.[8,102,103]

13. Immunomodulatory effects

Fosfomycin exerts immunomodulatory effects, mainly on lymphocyte and neutrophil function.[104] It has been suggested that fosfomycin, in addition to its antimicrobial activity, exhibits immunomodulatory effects on lipopolysaccharide-stimulated monocytes and T-lymphocytes. It appears that the action of fosfomycin on T-cells involves a suppression of interleukin (IL)-2 production.[105] Fosfomycin also has an immunomodulatory effect on B-cell activation. Honda et al. reported that fosfomycin suppresses both the production of leukotriene B4 (LTB4) from neutrophils and the expression of IL-8 mRNA by LTB4 from monocytes.[106]

Previous studies have shown that fosfomycin also affects the acute inflammatory cytokine response in vitro and in vivo.[107–109] Fosfomycin modulates the in vivo production of inflammatory cytokines, such as tumor necrosis factor (TNF)-α, IL-1β, and IL-6.[110] However, Sauermann et al.[111] evaluated the effect of fosfomycin on proinflammatory cytokines in healthy volunteers. They found that the concentrations of TNF-α, IL-1β, and IL-6 expressed as protein and mRNA levels were almost identical with and without fosfomycin.

Pérez Fernández et al.[112] found that fosfomycin enhances the phagocytic killing of invading pathogens by host cells. Similarly, Tullio et al.[113] reported that fosfomycin was able to induce the enhancement of the depressed phagocytic response of polymorphonuclear cells in patients on chronic hemodialysis and renal transplant recipients, restoring their primary functions in vitro against ESBL-producing *E. coli*. In addition, Krause et al.[114] investigated the effect of fosfomycin on neutrophil function. Fosfomycin incubation resulted in enhanced bactericidal ability, increased intracellular calcium concentrations, elevated extracellular reactive oxygen intermediate (ROI) production, and de-

creased chemotaxis, but did not affect intracellular ROI production and chemokinesis.

14. Conclusions

Fosfomycin is a bactericidal antibiotic with a broad spectrum of activity against a wide range of Gram-positive and Gram-negative bacteria. It presents good distribution into several tissues. It has a unique mechanism of action that may provide a synergistic effect to other antibiotics, including beta-lactams, aminoglycosides, and fluoroquinolones. Oral fosfomycin is used in the treatment of UTIs, mainly those caused by *E. coli* and *E. faecalis*. Intravenous fosfomycin has been administered in combination with other antibiotics for the treatment of nosocomial infections due to MDR Gram-positive and Gram-negative bacteria in daily doses ranging from 12 to 20 g. The intravenous administration of fosfomycin is associated with a low incidence of adverse effects. Further RCTs are needed to evaluate the efficacy of intravenous fosfomycin for the management of infections due to MDR pathogens.

Conflict of interest: The authors declare no funding and no conflict of interest. They also declare that ethical approval was not required.

References

1. Hendlin D, Stapley EO, Jackson M, Wallick H, Miller AK, Wolf FJ, et al. Phosphonomycin. A new antibiotic produced by strains of Streptomyces. *Science* 1969;**166**:122–3.
2. Falagas ME, Giannopoulou KP, Kokolakis GN, Rafailidis PI. Fosfomycin: use beyond urinary tract and gastrointestinal infections. *Clin Infect Dis* 2008;**46**:1069–77.
3. Woodruff HB, Mata JM, Hernández S, Mochales S, Rodríguez A, Stapley EO, et al. Fosfomycin: laboratory studies. *Chemotherapy* 1977;**23**(Suppl 1):1–22.
4. Suárez JE, Mendoza MC. Plasmid-encoded fosfomycin resistance. *Antimicrob Agents Chemother* 1991;**35**:791–5.
5. Kahan FM, Kahan JS, Cassidy PJ, Kropp H. The mechanism of action of fosfomycin (phosphonomycin). *Ann N Y Acad Sci* 1974;**235**:364–86.
6. Takahashi K, Kanno H. Synergistic activities of combination of beta lactams, fosfomycin, and tobramycin against *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother* 1984;**26**:789–91.
7. Chin NX, Neu NM, Neu HC. Synergy of fosfomycin with beta-lactam antibiotics against staphylococci and aerobic Gram-negative bacilli. *Drugs Exp Clin Res* 1986;**12**:943–7.
8. Okazaki M, Suzuki K, Asano N, Araki K, Shukuya N, Egami T, et al. Effectiveness of fosfomycin combined with other antimicrobial agents against multidrug-resistant *Pseudomonas aeruginosa* isolates using the efficacy time index assay. *J Infect Chemother* 2002;**8**:37–42.
9. Grayson ML. Kucers' the use of antibiotics, 6th ed., Melbourne, Australia: Hodder Arnold; 2010.
10. Segre G, Bianchi E, Cataldi A, Zannini G. Pharmacokinetic profile of fosfomycin trometamol (Monuril). *Eur Urol* 1987;**13**(Suppl 1):56–63.
11. Joukhadar C, Klein N, Dittrich P, Zeitlinger M, Geppert A, Skhirtladze K, et al. Target site penetration of fosfomycin in critically ill patients. *J Antimicrob Chemother* 2003;**51**:1247–52.
12. Legat FJ, Maier A, Dittrich P, Zenahlik P, Kern T, Nuhsbaumer S, et al. Penetration of fosfomycin into inflammatory lesions in patients with cellulitis or diabetic foot syndrome. *Antimicrob Agents Chemother* 2003;**47**:371–4.
13. Matzi V, Lindenmann J, Porubsky C, Kugler SA, Maier A, Dittrich P, et al. Extracellular concentrations of fosfomycin in lung tissue of septic patients. *J Antimicrob Chemother* 2010;**65**:995–8.
14. Schintler MV, Traunmüller F, Metzler J, Kreuzwirt G, Spendel S, Mauric O, et al. High fosfomycin concentrations in bone and peripheral soft tissue in diabetic patients presenting with bacterial foot infection. *J Antimicrob Chemother* 2009;**64**:574–8.
15. Frossard M, Joukhadar C, Erovic BM, Dittrich P, Mrass PE, Van Houte M, et al. Distribution and antimicrobial activity of fosfomycin in the interstitial fluid of human soft tissues. *Antimicrob Agents Chemother* 2000;**44**:2728–32.
16. Sauermann R, Karch R, Langenberger H, Kettenbach J, Mayer-Helm B, Petsch M, et al. Antibiotic abscess penetration: fosfomycin levels measured in pus and simulated concentration–time profiles. *Antimicrob Agents Chemother* 2005;**49**:4448–54.
17. Kuhnen E, Pfeifer G, Frenkel C. Penetration of fosfomycin into cerebrospinal fluid across non-inflamed and inflamed meninges. *Infection* 1987;**15**:422–4.
18. Sauermann R, Schwameis R, Fille M, Ligios ML, Zeitlinger M. Cerebrospinal fluid impairs antimicrobial activity of fosfomycin in vitro. *J Antimicrob Chemother* 2009;**64**:821–3.
19. Gobernado M. Fosfomycin. *Rev Esp Quimioter* 2003;**16**:15–40.
20. Pfausler B, Spiss H, Dittrich P, Zeitlinger M, Schmutzhard E, Joukhadar C. Concentrations of fosfomycin in the cerebrospinal fluid of neurointensive care patients with ventriculostomy-associated ventriculitis. *J Antimicrob Chemother* 2004;**53**:848–52.
21. Falagas ME, Maraki S, Karageorgopoulos DE, Kastoris AC, Kapaskelis A, Samonis G. Antimicrobial susceptibility of Gram-positive non-urinary isolates to fosfomycin. *Int J Antimicrob Agents* 2010;**35**:497–9.
22. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing. 20th informational supplement. Wayne, PA: CLSI; 2010.
23. de Cueto M, Lopez L, Hernandez JR, Morillo C, Pascual A. In vitro activity of fosfomycin against extended-spectrum-beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*: comparison of susceptibility testing procedures. *Antimicrob Agents Chemother* 2006;**50**:368–70.
24. Ribes S, Taberner F, Domenech A, Cabellos C, Tubau F, Liñares J, et al. Evaluation of fosfomycin alone and in combination with ceftriaxone or vancomycin in an experimental model of meningitis caused by two strains of cephalosporin-resistant *Streptococcus pneumoniae*. *J Antimicrob Chemother* 2006;**57**:931–6.
25. Banon Arias R, Garcia Lopez M, Pinedo Sanchez A. Time-kill evaluation of antimicrobial regimens against clinical isolates of penicillin-resistant *Streptococcus pneumoniae*. *J Chemother* 2001;**13**:535–40.
26. Mastouri M, Nour M, Ben Nejma M, Bouallegue O, Hammami M, Khedher M. Antibiotics resistance of methicillin-resistant *Staphylococcus aureus*: detection of the first glycopeptides low sensibility strains in Tunisia. *Pathol Biol (Paris)* 2006;**54**:33–6.
27. Allerberger F, Klare I. In-vitro activity of fosfomycin against vancomycin-resistant enterococci. *J Antimicrob Chemother* 1999;**43**:211–7.
28. Barry AL, Brown SD. Antibacterial spectrum of fosfomycin trometamol. *J Antimicrob Chemother* 1995;**35**:228–30.
29. de Cueto M, Hernández JR, López-Cerero L, Morillo C, Pascual A. Activity of fosfomycin against extended-spectrum beta-lactamase producing *Escherichia coli* and *Klebsiella pneumoniae*. *Enferm Infecc Microbiol Clin* 2006;**24**:613–6.
30. Falagas ME, Kastoris AC, Karageorgopoulos DE, Rafailidis PI. Fosfomycin for the treatment of infections caused by multidrug-resistant non-fermenting Gram-negative bacilli: a systematic review of microbiological, animal and clinical studies. *Int J Antimicrob Agents* 2009;**34**:111–20.
31. Martinez-Martinez L, Rodriguez G, Pascual A, Suárez AI, Perea EJ. In vitro activity of antimicrobial agent combinations against multiresistant *Acinetobacter baumannii*. *J Antimicrob Chemother* 1996;**38**:1107–8.
32. Pruekprasert P, Tunyapanit W. In vitro activity of fosfomycin–gentamicin, fosfomycin–ceftazidime, fosfomycin–imipenem and ceftazidime–gentamicin combinations against ceftazidime-resistant *Pseudomonas aeruginosa*. *Southeast Asian J Trop Med Public Health* 2005;**36**:1239–42.
33. Mirakhur A, Gallagher MJ, Ledson MJ, Hart CA, Walshaw MJ. Fosfomycin therapy for multiresistant *Pseudomonas aeruginosa* in cystic fibrosis. *J Cyst Fibros* 2003;**2**:19–24.
34. Altés Gutiérrez A, Rodríguez Noriega A. In vitro sensitivity of anaerobic bacteria to fosfomycin. *Chemotherapy* 1977;**23**(Suppl 1):51–7.
35. Falagas ME, Kastoris AC, Kapaskelis AM, Karageorgopoulos DE. Fosfomycin for the treatment of multidrug-resistant, including extended-spectrum beta-lactamase producing, *Enterobacteriaceae* infections: a systematic review. *Lancet Infect Dis* 2010;**10**:43–50.
36. Tharavichitkul P, Khantawa B, Bousoung V, Boonchoo M. Activity of fosfomycin against extended-spectrum-β-lactamase producing *Klebsiella pneumoniae* and *Escherichia coli* in Maharaj Nakorn Chiang Mai Hospital. *J Infect Dis Antimicrob Agents* 2005;**22**:121–6.
37. Giakkoupi P, Xanthaki A, Kanelopoulou M, Vlahaki A, Miriagou V, Kontou S, et al. VIM-1 Metallo-beta-lactamase producing *Klebsiella pneumoniae* strains in Greek hospitals. *J Clin Microbiol* 2003;**41**:3893–6.
38. Endimiani A, Patel G, Hujer KM, Swaminathan M, Perez F, Rice LB, et al. In vitro activity of fosfomycin against blaKPC-containing *Klebsiella pneumoniae* isolates, including those non-susceptible to tigecycline and/or colistin. *Antimicrob Agents Chemother* 2010;**54**:526–9.
39. Samonis G, Maraki S, Rafailidis PI, Kapaskelis A, Kastoris AC, Falagas ME. Antimicrobial susceptibility of Gram-negative nonurinary bacteria to fosfomycin and other antimicrobials. *Future Microbiol* 2010;**5**:961–70.
40. Rodríguez-Martínez JM, Ballesta S, Pascual A. Activity and penetration of fosfomycin, ciprofloxacin, amoxicillin/clavulanic acid and co-trimoxazole in *Escherichia coli* and *Pseudomonas aeruginosa* biofilms. *Int J Antimicrob Agents* 2007;**30**:366–8.
41. Monden K, Ando E, Iida M, Kumon H. Role of fosfomycin in a synergistic combination with ofloxacin against *Pseudomonas aeruginosa* growing in a biofilm. *J Infect Chemother* 2002;**8**:218–26.
42. Mikuniya T, Kato Y, Ida T, Maebashi K, Monden K, Kariyama R, et al. Treatment of *Pseudomonas aeruginosa* biofilms with a combination of fluoroquinolones and fosfomycin in a rat urinary tract infection model. *J Infect Chemother* 2007;**13**:285–90.
43. Cai Y, Fan Y, Wang R, An MM, Liang BB. Synergistic effects of aminoglycosides and fosfomycin on *Pseudomonas aeruginosa* in vitro and biofilm infections in a rat model. *J Antimicrob Chemother* 2009;**64**:563–6.
44. Kusachi S, Nagao J, Saida Y, Watanabe M, Okamoto Y, Asai K, et al. Antibiotic time-lag combination therapy with fosfomycin for postoperative intra-abdominal abscesses. *J Infect Chemother* 2011;**17**:91–6.
45. Etienne J, Gerbaud G, Courvalin P, Fleurette J. Plasmid-mediated resistance to fosfomycin in *Staphylococcus epidermidis*. *FEMS Microbiol Lett* 1989;**52**:133–7.
46. Beharry Z, Palzkill T. Functional analysis of active site residues of the fosfomycin resistance enzyme FosA from *Pseudomonas aeruginosa*. *J Biol Chem* 2005;**280**:17786–91.

47. Horii T, Kimura T, Sato K, Shibayama K, Ohta M. Emergence of fosfomycin-resistant isolates of Shiga-like toxin-producing *Escherichia coli* O26. *Antimicrob Agents Chemother* 1999;**43**:789–93.
48. García P, Arca P, Toyos JR, Suárez JE. Detection of fosfomycin resistance by the polymerase chain reaction and Western blotting. *J Antimicrob Chemother* 1994;**34**:955–63.
49. Arca P, Rico M, Braña AF, Villar CJ, Hardisson C, Suárez JE. Formation of an adduct between fosfomycin and glutathione: a new mechanism of antibiotic resistance in bacteria. *Antimicrob Agents Chemother* 1988;**32**:1552–6.
50. Arca P, Hardisson C, Suarez JE. Purification of a glutathione S-transferase that mediates fosfomycin resistance in bacteria. *Antimicrob Agents Chemother* 1990;**34**:844–8.
51. Cao M, Bernat BA, Wang Z, Armstrong RN, Helmann JD. FosB, a cysteine-dependent fosfomycin resistance protein under the control of sigma(W), an extracytoplasmic-function sigma factor in *Bacillus subtilis*. *J Bacteriol* 2001;**183**:2380–3.
52. Bernat BA, Laughlin LT, Armstrong RN. Fosfomycin resistance protein (FosA) is a manganese metalloglutathione transferase related to glyoxalase I and the extradiol dioxygenases. *Biochemistry* 1997;**36**:3050–5.
53. Rigsby RE, Fillgrove KL, Beihoffer LA, Armstrong RN. Fosfomycin resistance proteins: a nexus of glutathione transferases and epoxide hydrolases in a metalloenzyme superfamily. *Methods Enzymol* 2005;**401**:367–79.
54. Arca P, Reguera G, Hardisson C. Plasmid-encoded fosfomycin resistance in bacteria isolated from the urinary tract in a multicentre survey. *J Antimicrob Chemother* 1997;**40**:393–9.
55. Reeves D. Fosfomycin trometamol. *J Antimicrob Chemother* 1994;**34**:853–8.
56. Gold HS. Vancomycin-resistant enterococci: mechanisms and clinical observations. *Clin Infect Dis* 2001;**33**:210–9.
57. Jones RN, Anderegg TR, Swenson JM. Quality control guidelines for testing Gram-negative control strains with polymyxin B and colistin (polymyxin E) by standardized methods. *J Clin Microbiol* 2005;**43**:925–7.
58. Rudenko N, Dorofeyev A. Prevention of recurrent lower urinary tract infections by long-term administration of fosfomycin trometamol. Double blind, randomized, parallel group, placebo controlled study. *Arzneimittelforschung* 2005;**55**:420–7.
59. Falagas ME, Vouloumanou EK, Togias AG, Karadima M, Kapaskelis AM, Rafailidis PI, et al. Fosfomycin versus other antibiotics for the treatment of cystitis: a meta-analysis of randomized controlled trials. *J Antimicrob Chemother* 2010;**65**:1862–77.
60. Pullukcu H, Tasbakan M, Sipahi OR, Yamazhan T, Aydemir S, Ulusoy S. Fosfomycin in the treatment of extended spectrum beta-lactamase-producing *Escherichia coli*-related lower urinary tract infections. *Int J Antimicrob Agents* 2007;**29**:62–5.
61. Rodríguez-Baño J, Alcalá JC, Cisneros JM, Grill F, Oliver A, Horcajada JP, et al. Community infections caused by extended-spectrum beta-lactamase-producing *Escherichia coli*. *Arch Intern Med* 2008;**168**:1897–902.
62. Stein GE. Fosfomycin tromethamine: single-dose treatment of acute cystitis. *Int J Fertil Womens Med* 1999;**44**:104–9.
63. Schito GC. Why fosfomycin trometamol as first line therapy for uncomplicated UTI? *Int J Antimicrob Agents* 2003;**22**(Suppl 2):79–83.
64. Souli M, Galani I, Antoniadou A, Papadomichelakis E, Poulakou G, Panagea T, et al. An outbreak of infection due to beta-lactamase *Klebsiella pneumoniae* carbapenemase 2-producing *K. pneumoniae* in a Greek University Hospital: molecular characterization, epidemiology, and outcomes. *Clin Infect Dis* 2010;**50**:364–73.
65. Michalopoulos A, Virtzili S, Rafailidis P, Chalevelakis G, Damala M, Falagas ME. Intravenous fosfomycin for the treatment of nosocomial infections due to carbapenem-resistant *Klebsiella pneumoniae* in critically ill patients: a prospective evaluation. *Clin Microbiol Infect* 2010;**16**:184–6.
66. Yamaguchi Y, Hanaki H, Yanagisawa C, Ikeda-Dantsuji Y, Hashimoto T, Yazaki H, et al. Characterization of beta-lactam antibiotic-induced vancomycin-resistant MRSA (BIVR) in a patient with septicemia during long-term vancomycin administration. *J Infect Chemother* 2009;**15**:274–8.
67. Forestier F, Salvanet-Bouccara A, Leveques D, Junes P, Rakotondrainy C, Dublanchet A, et al. Ocular penetration kinetics of fosfomycin administered as a one-hour infusion. *Eur J Ophthalmol* 1996;**6**:137–42.
68. Popovic M, Steinort D, Pillai S, Joukhadar C. Fosfomycin: an old, new friend? *Eur J Clin Microbiol Infect Dis* 2010;**29**:127–42.
69. Meissner A, Haag R, Rahmanzadeh R. Adjuvant fosfomycin medication in chronic osteomyelitis. *Infection* 1989;**17**:146–51.
70. Florent A, Chichmanian RM, Cua E, Pulcini C. Adverse events associated with intravenous fosfomycin. *Int J Antimicrob Agents* 2011;**37**:82–3.
71. Alvarez R, Adan A, Martinez JA, Casale A, Miro JM. Haematogenous *Serratia marcescens* endophthalmitis in an HIV-infected intravenous drug addict. *Infection* 1990;**18**:29–30.
72. Boulard G, Quentin C, Scontrini G, Dautheribes M, Pouguet P, Sabathie M. Treatment of ventriculitis caused by *Staphylococcus epidermidis* on equipment with the combination of fosfomycin and an aminoglycoside. Course of ventricular levels of fosfomycin. *Pathol Biol (Paris)* 1983;**31**:525–7.
73. Bureau-Chalot F, Piednoir E, Bazin A, Brasme L, Bajolet O. Postoperative spondylodiskitis due to *Stomatococcus mucilaginosus* in an immunocompetent patient. *Scand J Infect Dis* 2003;**35**:146–7.
74. Gillard J, Boutoille D, Varin S, Asseray N, Berthelot JM, Maugars Y. Suspected disk space infection with negative microbiological tests—report of eight cases and comparison with documented pyogenic discitis. *Joint Bone Spine* 2005;**72**:156–62.
75. Guerin F, Henegar C, Spiridon G, Launay O, Salmon-Ceron D, Poyart C. Bacterial prostatitis due to *Pseudomonas aeruginosa* harbouring the bla-VIM-2 metallo-β-lactamase gene from Saudi Arabia. *J Antimicrob Chemother* 2005;**56**:601–2.
76. May T, Weber M, Gérard A, Schmit JL, Voiriot P, Czorny A, et al. Treatment of post-traumatic and post-neurosurgical bacterial meningitis with ceftriaxone alone or in combination with fosfomycin. *Pathol Biol (Paris)* 1987;**35**(5 Pt 2):839–42.
77. Nakayama M, Tsunoda K, Igarashi M, Nishikawa K, Okazaki K. A case of toxic shock syndrome induced by MRSA after sinus surgery. *Masui* 1996;**45**:994–7.
78. Nissen LR, Jacobsen J, Ravn TJ, Wahlgreen C, Auning-Hansen H. Fosfomycin–ampicillin versus gentamicin–ampicillin in the treatment of critically ill patients with pneumonia. *Infection* 1986;**14**:246–9.
79. Ortler M, Luef G, Kofler A, Bauer G, Twerdy K. Deep wound infection after vagus nerve stimulator implantation: treatment without removal of the device. *Epilepsia* 2001;**42**:133–5.
80. Portier H, Kazmierczak A, Lucht F, Tremeaux JC, Chavanet P, Duez JM. Cefotaxime in combination with other antibiotics for the treatment of severe methicillin-resistant staphylococcal infections. *Infection* 1985;**13**(Suppl 1):S123–8.
81. Roualdes G, Lartigue C, Boudigue MD, Maissin F. Infection of the valves of CSF shunts: results of local and general antibiotic treatment in 6 cases. *Neurochirurgie* 1985;**31**:390–4.
82. Silbermann MH, Gyssens IC, Wielenga JJ, Endtz HP, Löwenberg B. A patient with acute leukemia and meningitis caused by *Staphylococcus epidermidis* treated with fosfomycin. *Ned Tijdschr Geneeskd* 1995;**139**:2498–501.
83. Ueda T, Masaoka T, Shibata H, Nagai K, Kanamaru A, Horiuchi A, et al. Clinical evaluation of high dose intravenous injection of fosfomycin on the severe infections associated with the treatment of haematological disorders. *Jpn J Antibiot* 1983;**36**:311–5.
84. Zink PM, Schick D, Trappe AE. Non-surgical management of an infected ventriculo-atrial shunt. *Neurochirurgia (Stuttg)* 1989;**32**:61–4.
85. Ishizaka K, Kobayashi S, Machida T, Yoshida K. Randomized prospective comparison of fosfomycin and cefotiam for prevention of postoperative infection following urological surgery. *J Infect Chemother* 2007;**13**:324–31.
86. Andåker L, Burman LG, Eklund A, Graffner H, Hansson J, Hellberg R, et al. Fosfomycin/metronidazole compared with doxycycline/metronidazole for the prophylaxis of infection after elective colorectal surgery: a randomised double-blind multicentre trial in 517 patients. *Eur J Surg* 1992;**158**:181–5.
87. Andåker L, Höjer H, Kihlström E, Lindhagen J. Stratified duration of prophylactic antimicrobial treatment in emergency abdominal surgery. Metronidazole–fosfomycin vs. metronidazole–gentamicin in 381 patients. *Acta Chir Scand* 1987;**153**:185–92.
88. Lebreton P, Vergnaud M, Zerr C, Nigam M, Kaladji C, Quesnel J. Antibiotic prophylaxis using a combination of pefloxacin and fosfomycin in heart surgery with CEC (extracorporeal circulation) in patients allergic to beta-lactams. *Cah Anesthesiol* 1989;**37**:77–87.
89. Lindhagen J, Andåker L, Höjer H. Comparison of systemic prophylaxis with metronidazole/placebo and metronidazole/fosfomycin in colorectal surgery. A clinical study demonstrating the need for additional anti-aerobic prophylactic cover. *Acta Chir Scand* 1984;**150**:317–23.
90. Nøhr M, Andersen JC, Juul-Jensen KE. Prophylactic single-dose fosfomycin and metronidazole compared with neomycin, bacitracin, metronidazole and ampicillin in elective colorectal operations. *Acta Chir Scand* 1990;**156**:223–30.
91. Shinagawa N, Mizuno I, Fukui T, Takeyama H, Yasuda A, Matsumoto K, et al. Prophylactic effect of fosfomycin on postoperative infection in gastroenterological surgery. *Jpn J Antibiot* 2006;**59**:417–27.
92. Sánchez-Morillas L, Pérez-Ezquerra PR, Reaño-Martos M, Mayorga C, Laguna-Martínez JJ. Anaphylaxis induced by fosfomycin. *Ann Allergy Asthma Immunol* 2010;**105**:241.
93. Patel SS, Balfour JA, Bryson HM. Fosfomycin tromethamine. A review of its antibacterial activity, pharmacokinetic properties and therapeutic efficacy as a single-dose oral treatment for acute uncomplicated lower urinary tract infections. *Drugs* 1997;**53**:637–56.
94. Bedirdjian JP, Morin JP, Fouchet B, Fillastre JP. Effect of fosfomycin on respiration by rat kidney mitochondria. *Minerva Med* 1978;**69**:4079–86.
95. Mayama T, Yokota M, Shimatani I, Ohyagi H. Analysis of oral fosfomycin calcium (Fosmicin) side-effects after marketing. *Int J Clin Pharmacol Ther Toxicol* 1993;**31**:77–82.
96. Available at: http://www.drugs.com/drug-interactions/fosfomycin.html [accessed day September 15, 2011].
97. Ferrara A, Dos Santos C, Cimbro M, Gialdroni Grassi G. Effect of different combinations of sparfloxacin, oxacillin, and fosfomycin against methicillin-resistant staphylococci. *Eur J Clin Microbiol Infect Dis* 1997;**16**:535–7.
98. Komatsuzawa H, Suzuki J, Sugai M, Miyake Y, Suginaka H. Effect of combination of oxacillin and non-beta-lactam antibiotics on methicillin-resistant *Staphylococcus aureus*. *J Antimicrob Chemother* 1994;**33**:1155–63.
99. Sahuquillo Arce JM, Colombo Gainza E, Gil Brusola A, Ortiz Estévez R, Cantón E, Gobernado M. In vitro activity of linezolid in combination with doxycycline, fosfomycin, levofloxacin, rifampicin and vancomycin against methicillin susceptible *Staphylococcus aureus*. *Rev Esp Quimioter* 2006;**19**:252–7.
100. Rice LB, Eliopoulos CT, Yao JD, Eliopoulos GM, Moellering Jr RC. In vivo activity of the combination of daptomycin and fosfomycin compared with daptomycin alone against a strain of *Enterococcus faecalis* with high-level gentamicin

resistance in the rat endocarditis model. *Diagn Microbiol Infect Dis* 1992;**15**:173–6.
101. Yu XH, Song XJ, Cai Y, Liang BB, Lin DF, Wang R. In vitro activity of two old antibiotics against clinical isolates of methicillin-resistant *Staphylococcus aureus*. *J Antibiot (Tokyo)* 2010;**63**:657–9.
102. Olay TA, Rodriguez A, Oliver LE, Vicente MV, Quecedo MC. Interaction of fosfomycin with other antimicrobial agents: in vitro and vivo studies. *J Antimicrob Chemother* 1978;**4**:569–76.
103. Hayami H, Goto T, Kawahara M, Ohi Y. Activities of β-lactams, fluoroquinolones, amikacin and fosfomycin alone and in combination against *Pseudomonas aeruginosa* isolated from complicated urinary tract infections. *J Infect Chemother* 1999;**5**:130–8.
104. Roussos N, Karageorgopoulos DE, Samonis G, Falagas ME. Clinical significance of the pharmacokinetic and pharmacodynamic characteristics of fosfomycin for the treatment of patients with systemic infections. *J Antimicrob Agents* 2009;**34**:506–15.
105. Morikawa K, Oseko F, Morikawa S, Sawada M. Immunosuppressive activity of fosfomycin on human T-lymphocyte function in vitro. *Antimicrob Agents Chemother* 1993;**37**:2684–7.
106. Honda J, Okubo Y, Kusaba M, Kumagai M, Saruwatari N, Oizumi K. Fosfomycin (FOM: 1 R-2S-epoxypropylphosphonic acid) suppress the production of IL-8 from monocytes via the suppression of neutrophil function. *Immunopharmacology* 1998;**39**:149–55.
107. Matsumoto T, Tateda K, Miyazaki S, Furuya N, Ohno A, Ishii Y, et al. Immunomodulating effect of fosfomycin on gut-derived sepsis caused by *Pseudomonas aeruginosa* in mice. *Antimicrob Agents Chemother* 1997;**41**:308–13.
108. Morikawa K, Watabe H, Araake M, Morikawa S. Modulatory effect of antibiotics on cytokine production by human monocytes in vitro. *Antimicrob Agents Chemother* 1996;**40**:1366–70.
109. Morikawa K, Zhang J, Nonaka M, Morikawa S. Modulatory effect of macrolide antibiotics on the Th1- and Th2-type cytokine production. *Int J Antimicrob Agents* 2002;**19**:53–9.
110. Matsumoto T, Tateda K, Miyazaki S, Furuya N, Ohno A, Ishii Y, et al. Fosfomycin alters lipopolysaccharide-induced inflammatory cytokine production in mice. *Antimicrob Agents Chemother* 1999;**43**:697–8.
111. Sauermann R, Marsik C, Steiner I, Seir K, Cvitko T, Zeitlinger M, et al. Immunomodulatory effects of fosfomycin in experimental human endotoxemia. *Antimicrob Agents Chemother* 2007;**51**:1879–81.
112. Pérez Fernández P, Herrera I, Martínez P, Gómez-Lus ML, Prieto J. Enhancement of the susceptibility of *Staphylococcus aureus* to phagocytosis after treatment with fosfomycin compared with other antimicrobial agents. *Chemotherapy* 1995;**41**:45–9.
113. Tullio V, Cuffini AM, Banche G, Mandras N, Allizond V, Roana J, et al. Role of fosfomycin tromethamine in modulating non-specific defence mechanisms in chronic uremic patients towards ESBL-producing *Escherichia coli*. *Int J Immunopathol Pharmacol* 2008;**21**:153–60.
114. Krause R, Patruta S, Daxböck F, Fladerer P, Wenisch C. The effect of fosfomycin on neutrophil function. *J Antimicrob Chemother* 2001;**47**:141–6.