Clinical Microbiology and Infection 23 (2017) 363–372

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Systematic review

Intravenous fosfomycin—back to the future. Systematic review and meta-analysis of the clinical literature

B. Grabein [1], W. Graninger [2], J. Rodríguez Baño [3,4], A. Dinh [5], D.B. Liesenfeld [6,*]

[1] Department of Clinical Microbiology and Hospital Hygiene, Munich University Hospital, Munich, Germany
[2] Institute for Infectiology, Karl Landsteiner Society, Vienna, Austria
[3] Unidad Clínica de Enfermedades Infecciosas, Microbiología y Medicina Preventiva, Hospital Universitarios Virgen Macarena y Virgen del Rocío, Departamento de Medicina, Universidad de Sevilla—IBIS, Sevilla, Spain
[4] Spanish Network for Research in Infectious Diseases, Instituto de Salud Carlos III, Madrid, Spain
[5] Infectious Disease Unit, R. Poincaré University Hospital, Garches, AP-HP, Versailles Saint Quentin University, Garches, France
[6] InfectoPharm Arzneimittel und Consilium GmbH, Heppenheim, Germany

ARTICLE INFO

Article history:
Received 24 August 2016
Received in revised form
12 November 2016
Accepted 3 December 2016
Available online 9 December 2016

Editor: M. Paul

Keywords:
Clinical outcome
Fosfomycin
Intravenous
Meta-analysis
Multi drug resistance
Systematic review

ABSTRACT

Objectives: We conducted a systematic review and meta-analysis to summarize the clinical evidence and usage patterns of intravenous fosfomycin from its development to the present time.
Methods: PubMed, the Cochrane Library and local journals were searched for relevant studies reporting aggregated data of intravenous fosfomycin use in adults and children, with no restrictions regarding study design. Single case reports were excluded. Data were systematically abstracted for all included studies. Clinical and microbiological efficacy from randomized controlled and comparative observational studies were synthesized using meta-analysis to calculate pooled effect sizes.
Results: In all, 128 studies on intravenous fosfomycin in 5527 patients were evaluated. Fosfomycin was predominantly used for sepsis/bacteraemia, urinary tract, respiratory tract, bone and joint, and central nervous system infections. No difference in clinical (OR 1.44, 95% CI 0.96–2.15) or microbiological (OR 1.28, 95% CI 0.82–2.01) efficacy between fosfomycin and other antibiotics was observed in comparative trials. The pooled estimate for resistance development during fosfomycin monotherapy was 3.4% (95% CI 1.8%–5.1%). Fosfomycin showed a favourable safety profile, with generally mild adverse events not requiring discontinuation of treatment. Included studies explored intravenous fosfomycin as an anti-staphylococcal agent in monotherapy and combination therapy, whereas studies from 1990 focused on combination therapy (fosfoymcin + β-lactams or aminoglycosides) for challenging infections frequently caused by multidrug-resistant organisms.
Conclusion: Intravenous fosfomycin can play a vital role in the antibiotic armamentarium, given its long history of effective and safe use. However, well-designed randomized controlled trials are still desired.
B. Grabein, Clin Microbiol Infect 2017;23:363

Introduction

Fosfomycin is a broad-spectrum, bactericidal antibiotic discovered in 1969 [1]. It is the sole member of the epoxide group of antibiotics and inhibits peptidoglycan formation at an earlier step than β-lactams. Intravenous fosfomycin was initially registered in various European (Spain, Germany, France) and non-European (Japan) countries. The clinical use of intravenous fosfomycin has remained at relatively constant but low levels. Interest in intravenous fosfomycin has renewed in the twenty-first century, as it remains active against many problematic pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA) [2], glycopeptide-resistant enterococci [3,4], and multidrug-resistant (MDR) enterobacteria [5]. Fosfomycin is active against a wide range of Gram-positive and Gram-negative species, but shows only very limited activity against anaerobic species, most importantly *Bacteroides*, as well as against selected Gram-negative species such as *Acinetobacter baumannii* or

* Corresponding author. D.B. Liesenfeld, InfectoPharm Arzneimittel und Consilium GmbH, Von-Humboldt-Straße 1, 64646 Heppenheim, Germany.
E-mail address: david.liesenfeld@infectopharm.de (D.B. Liesenfeld).

http://dx.doi.org/10.1016/j.cmi.2016.12.005
1198-743X/

Burkholderia spp. [6,7]. Fosfomycin is regarded as an antibiotic with attractive pharmacokinetic properties, explaining its potential value in complicated and frequently deep-seated infections such as infections of the central nervous system (CNS) [8,9], bone and joints [10], lungs [11], and soft tissues [12], as well as sepsis [13,14]. Development of resistance to fosfomycin is a concern, but the clinical relevance and determinants are not well understood. This review aims to summarize the available evidence on intravenous fosfomycin. Furthermore, inclusion of clinical reports from the developmental era of fosfomycin will make these publications globally available for the first time. This study will also describe clinical patterns of intravenous fosfomycin use and help to identify gaps for future clinical research.

Materials and methods

Identification of studies

We searched PubMed and the Cochrane Library without any language restrictions until July 2016 to identify studies on human clinical exposure to intravenous fosfomycin. Electronic search strategies are provided in the Supplementary material (Data S1). Additionally, we identified records by a hand search of local journals not indexed in the above-mentioned medical databases.

Inclusion criteria and study selection

Only studies reporting aggregated data of intravenous fosfomycin use in patients were included. Studies reporting on intravenous use in addition to other routes of administration were also included, but data abstracted separately by each route of administration, if possible. Single case reports, animal studies and *in vitro* data were excluded. The following treatment indications were accepted: osteomyelitis, meningitis, encephalitis, cerebral abscess, urinary tract infections (UTI), respiratory tract infections (RTI), pulmonary abscesses, perioperative infections, skin infections, soft-tissue infections, burn-associated infections, diabetic foot infections, intra-abdominal infections, sepsis/bacteraemia, endocarditis, and ear, nose and throat infections.

Data extraction

The following data were abstracted from the full texts of included articles: study design, number of patients treated with fosfomycin, patients' age and gender, treatment indication(s), monotherapy or combination therapy (at least 1 day of dual therapy), duration of treatment, control group (for comparative studies), mean daily dose of fosfomycin (an adult body weight of 70 kg was assumed for conversion from doses in g to doses in mg/kg), clinical efficacy (evaluated according to the definitions used in each individual study), organisms isolated, microbiological efficacy, and development of resistance (as per definition of individual authors) during fosfomycin monotherapy, as well as safety data. For each continuous variable, the mean ± standard deviation was weighted by the number of patients to take account of study sizes.

Quality assessment

Due to the broad inclusion criteria and scope, a high level of heterogeneity between studies was anticipated. Non-comparative studies (inherently high risk of bias) were therefore not assessed for quality and not used for meta-analysis. Quality of comparative trials (randomized controlled and comparative observational studies) was assessed using a grading scheme by the National Institute of Health (NIH) (http://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/rct). According to the scheme, various parameters of quality such as presence and method of randomization, treatment allocation, single and double blinding, absence of differences in patient populations, overall and differential dropout rate, protocol adherence, similar background interventions, outcome assessment, sample size, prespecified subgroup analysis and intention-to-treat analysis were checked. Studies earned one point for the presence of each quality criterion and were graded as poor (1–4 points), poor–fair (5 points), fair (6–8 points), fair–good (9 points) or good (10–14 points) by three independent assessors (BG, WG, DBL). In case of non-agreement, all the assessors discussed studies to reach consensus.

Data analysis and statistics

Analysis of clinical and microbiological efficacy (meta-analysis). Only data from studies comparing fosfomycin against other antibiotics were included into a meta-analysis (random effects model) of clinical and microbiological efficacy using OR as the effect size estimate. Odds ratios >1 favoured fosfomycin therapy. Only crude effect sizes were used, as studies did not report on adjusted efficacy outcomes. To assess the effect of study quality on outcomes, we performed a sensitivity analysis including all comparative trials versus trials with poor quality excluded. Additionally, an exploratory analysis was conducted to explore associations of covariates with clinical efficacy (see Supplementary material, Data S2).

All analyses were carried out in the statistical software R 3.3.1. The METAFOR package was used to run meta-analyses and meta-regressions [15].

Analysis of safety data. All studies reporting adverse reactions were included into analysis of safety data. Adverse events were abstracted and rated as non-serious or serious as per listing on the EudraVigilance Expert Working Group Important Medical Events list version 18.1.

Results

Of 559 records identified by systematic literature search, 128 studies fulfilled the inclusion criteria and were subject to review and systematic data abstraction (see Fig. 1). Studies excluded at the abstract or full text stages were mostly single case reports or reported on oral fosfomycin only (see Supplementary material, Data S3 for a full list studies and abstracted data).

Patterns of clinical use

Patient population. The 128 studies included 5527 patients treated with intravenous fosfomycin. Most studies originated from France ($n = 38$), Germany and Austria ($n = 31$), Japan ($n = 24$) or Spain ($n = 20$). A majority of the studies ($n = 84$) were published before 1989, i.e. before the formal adoption of EU guidelines on good clinical practice. Twenty-eight of the 128 studies (21.9%) exclusively reported on paediatric populations ($n = 819$) [16–43]. Seven case series reported exclusively on newborns and infants receiving fosfomycin for neonatal sepsis, meningitis or severe UTI. Fifteen additional studies included both children and adults [44–58]. Seven studies focused on the use of fosfomycin in patients with haematological malignancies [18,30,59–63].

Quality of studies. Almost half of the reports (61/128; 48%) were retrospective case series and only a minority of studies were comparative (six non-randomized controlled trials and three case-control studies; 9/128; 7%) or randomized controlled (8/128; 6%). Comparative studies scored an average of 6/14 quality points, indicating low to average quality, with high variability across studies (see Table 1 and see Supplementary material, Data for individual scores).

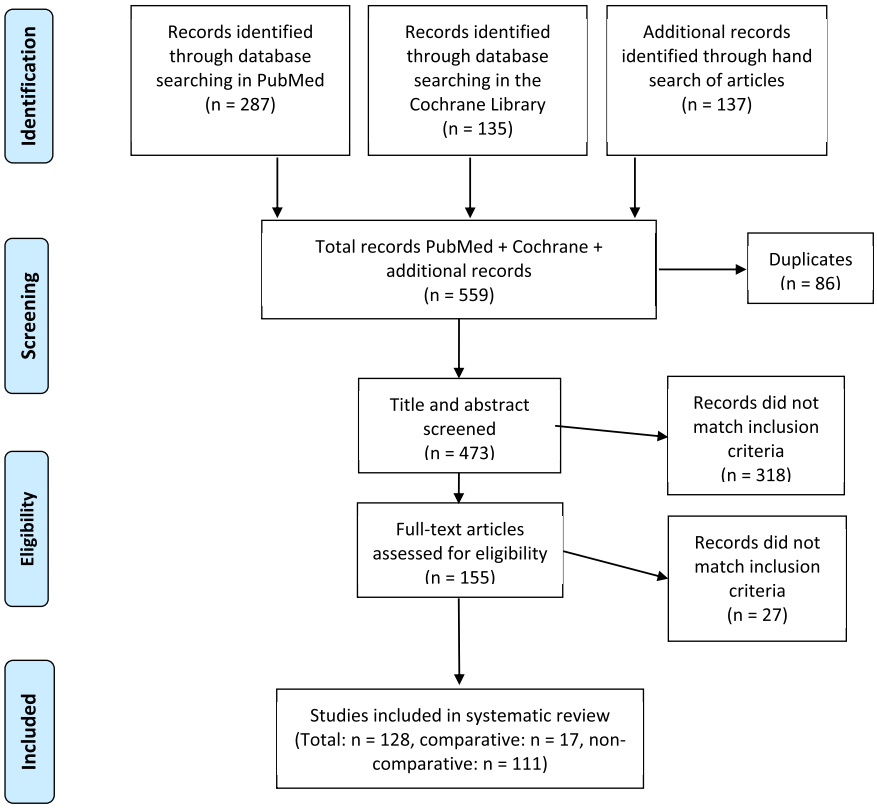

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart describing the search strategy.

Most studies lacked statistical power, randomization or blinding procedures, adequate description of randomization procedures or treatment allocation, and appropriate measures to control for possible confounding factors (observational studies).

Indications and isolated pathogens. More than 75% of all patients (4279/5527; 77%) were treated for five main indications, sepsis/bacteraemia, RTI (mostly pneumonia), UTI, bone/joint infections (mostly osteomyelitis) and CNS infections (Fig. 2a).

A total of 3495 pathogens were isolated in all studies combined. Fosfomycin was most often used against staphylococci (1408 isolates), predominantly *Staphylococcus aureus* (1062 isolates), *Escherichia coli* (544 isolates), *Pseudomonas* spp. (465 isolates), *Streptococcus* spp. (252 isolates) and *Klebsiella* spp. (218 isolates) (Fig. 2b). Fourteen studies placed emphasis on pathogens with pre-existing resistance to various antibiotic classes such as MRSA or methicillin-resistant *Staphylococcus epidermidis* [14,75,77–82] or carbapenem-resistant and MDR Gram-negative species (resistance status reported as defined by the respective authors) [44,67,74,83–85]. Studies on MDR Gram-negative species were all published after 2010.

Dosing and therapy regimens. Fosfomycin dosing, averaged over all patients, varied considerably across studies and countries. Dosing in Europe was consistent, with average daily doses of 181 mg/kg (12.7 g) for France, 182 mg/kg (12.7 g) for Germany/Austria, and 220 mg/kg (15.7 g) for Spain, typically divided into two or three equal doses. In contrast, dosing was much lower in Japan, with an average of 56 mg/kg (3.9 g) per day. Few studies reported on high-dose (>20 g / >285 mg/kg) treatment [20,32,57,85–87]. With respect to paediatric populations, authors reported daily doses based on body weight, mostly in the range 100–200 mg/kg (lowest: 50 mg/kg; highest: 500 mg/kg).

More studies reported on fosfomycin combination therapy (73 studies, 2675 patients) than monotherapy (44 studies, 1757 patients). Monotherapy was used for all major indications, though in osteomyelitis and UTI fosfomycin was used as monotherapy in a greater proportion of patients (604/1693 patients; 36%) than combination therapy (388/2493 patients; 16%). Monotherapy studies were almost exclusively published before 1990; studies on combination therapy thereafter (see Supplementary material, Fig. S1). Combination therapy was most often implemented with a β-lactam, i.e. cephalosporins (1066 patients), penicillins (533 patients), carbapenems (150 patients), or an aminoglycoside (254 patients).

Clinical efficacy

Ten studies (seven randomized) comparing the clinical efficacy of intravenous fosfomycin against other antibiotics were included into a meta-analysis, corresponding to 315 patients treated with fosfomycin. We did not observe a difference in clinical efficacy between fosfomycin and respective comparators (OR 1.44, 95% CI 0.96–2.15) irrespective of monotherapy (OR 1.41, 95% CI 0.83–2.39) or combination therapy (OR 1.48, 95% CI 0.81–2.71). The same results were obtained when studies with poor quality were excluded (OR 1.45, 95% CI 0.94–2.24). Among the six studies with fair or good study quality, fosfomycin combination therapy was used against RTIs/pneumonias (three of three studies). Monotherapy was used against UTIs (two or three studies), or RTIs (one study of three). No heterogeneity was observed in any meta-analyses (Fig. 3). For exploratory analyses see Supplementary material and Tables S2–S3.

Microbiology

Microbiological efficacy. The study of Albano et al. did not report any microbiological efficacy data and was therefore excluded [72]. Pooled analysis of the remaining nine comparative studies did not indicate any difference between fosfomycin and its comparators (OR

Table 1
Summary of studies comparing intravenous fosfomycin therapy (either monotherapy or combination) against another therapy regimen

Author, yr, country	Design	Patients, *n*	Infection	Isolated pathogens	Fosfomycin treatment	Comparator	Clinical cure	Microbio. cure	Quality
Sano, 1979 [64], Japan	RCT	107, adults	UTI	*Pseudomonas* spp. (mostly *Pseudomonas aeruginosa*), *Proteus* spp. (mostly *Proteus mirabilis*)	2 × 2 g/day fosfomycin	2 × 2g/day sulbencillin	33/57 (56%) vs. 27/50 (54%)	23/57 (40%) vs. 20/50 (40%)	Good
Kobashi, 2002 [65], Japan	RCT	41, adults	Moderate pneumonia[d]	*Klebsiella pneumoniae* (4), *Streptococcus pneumoniae* (4), MSSA (4), *P. aeruginosa* (3), MRSA (2), *Klebsiella oxytoca* (2), *Haemophilus influenzae*, *Enterococcus cloacae*, *Serratia marcescens*, *Streptococcus milleri*, *Acinetobacter baumannii* (1 each)	2 × 2 g/day fosfomycin + 2 × 1 g/day sulbactam/cefoperazone	2 × 1 g/day sulbactam/cefoperazone	17/18 (94%) vs. 15/17 (88%)	5/10 (50%) vs. 5/9 (56%)	Fair-good
Shimokata, 1988 [66], Japan	RCT	53, adults	RTI (mostly pneumonia)	*H. influenzae* (4), *K. pneumoniae* (3), *Staphylococcus aureus* (2), *S. agalactiae* (2), *Streptococcus viridans* (2), *Klebsiella* sp., *P. aeruginosa, Staphylococcus epidermidis, Haemophilus parainfluenzae, Enterococcus faecium, Enterobacter aerogenes, Streptococcus pneumoniae* (1 each)	2 × 1-2g/day fosfomycin + 2 × 1–2 g/day cefotaxime	cefotaxime	33/41 (80%) vs. 27/32 (84%)	10/11 (91%) vs. 4/4 (100%)	Poor-fair
Hiraoka, 1996 [61], Japan	RCT (Supplement)	161, age: NA	Bacteraemia/SepsisPneumonia	Not reported	2 2 g/day fosfomycin + 2 × 1–2g/day sulbactam/cefoperazone	Sequence 1: Fos -> Sul/CefSequence 2: Sul/Cef -> Fos	45/76 (59%) vs. 30/69 (43%)	Not reported	Poor-fair
Sirijatuphat, 2014 [67], Thailand	RCT	104, adults	*A. baumannii* infections (78% pneumonia)	Carbapenem-resistant *A. baumannii*	2 × 4 g/day fosfomycin + 5 mg/kg/day colistin (base activity)	5 mg/kg/day colistin (base activity)	30/47 (64%) vs. 27/47 (57%)	47/47 (100%) vs. 38/47 (81%); p 0.01	Fair-good
Ode, 1988 [68], Sweden	RCT	38, adults	Pyelonephritis	*Escherichia coli* (30), *Klebsiella* spp. (2), *Proteus vulgaris, P. aeruginosa, Staphylococcus aureus, Enterococcus* sp. (1 each)	2 × 8 g/day fosfomycin[a]	3 × 2 g ampicillin	7/16 (44%) vs. 6/22 (27%)	7/16 (44%) vs. 6/22 (27%)	Fair
Nissen, 1986 [69], Denmark	RCT	32, adults	Severe[d] acute pneumonia	Coagulase neg. staphylococci (9), *Streptococcus pneumoniae* (6), *Streptococcus* spp. (4), *Moraxella catarrhalis* (4), *Escherichia coli* (7), *K. pneumoniae* (4), *Haemophilus influenzae* (2), *Enterococcus cloacae* (1), *P. aeruginosa* (3)	3 × 4 g/day fosfomycin + 3 × 80 mg gentamicin[b]	4 × 1 g/day ampicillin + 3 × 80 mg gentamicin	10/17 (59%) vs. 7/15 (47%)	87.5% vs. 90% (no absolute numbers)	Fair
Zhang, 2003 [70], China	RCT	118, adults	lower RTI[d]	*Streptococcus pneumoniae* (18), *K. pneumoniae* (17), *Escherichia coli* (16), *Staphylococcus epidermidis* (9), *Haemophilus verdigris* (9), *Staphylococcus haemolyticus* (8), *P. aeruginosa* (7), *Staphylococcus aureus* (3), *Acinetobacter* spp. (3)	8 g/day fosfomycin	4 g/day ceftriaxone	49/59 (83%) vs. 45/59 (76%)	75/90 (83%) vs. 68/85 (80%)	Fair
Otsuka, 1994 [71], Japan	Non-randomized controlled study	47, adults (15 cancer patients)	Primarily RTI (50% pneumonia)	MRSA (23), MRSA + secondary pathogen (39). Secondary pathogens: *P. aeruginosa* (14), *K. pneumoniae* (5), *Enterococcus* spp. (5) and others	2 × 2-4 g/day fosfomycin + 2 × 2g/day cefmetazole	2 × 2-4 g/day fosfomycin + 2 × 2 g/day flomocef	16/22 (73%) vs. 14/22 (64%)	11/22 (50%) vs. 11/25 (44%)	Poor-fair
Albano, 1978 [72], Italy	Case–control study	64, pregnant women	Obstetric infections	Not reported	fosfomycin (dose not reported)	cefapirin (dose not reported)	35/38 (92%) vs. 22/26 (85%)	Not reported	Poor

Baron, 1987 [73], France	Case–control study	35, adults and children	primarily sepsis	MSSA	237 mg/kg/day fosfomycin + 145 mg/kg/day Penicillin M	3.6 mg/kg/day gentamycin + 113 mg/kg/day Penicillin M	16/17 (94%) vs. 14/18 (78%)	same as clinical	Poor-fair
Apisarnthanarak, 2012 [74], Thailand	Case–control study	49, adults	HAP, VAP	Carbapenem resistant *P. aeruginosa*	Fosfomycin + Doripenem (dose not reported)	Fosfomycin + Colistin (dose not reported)	15/25 (60%) vs. 14/25 (56%)	18/25 (72%) vs. 15/24 (63%)	Poor
Matsumoto, 1993 [75], Japan	Non-randomized controlled study	19, adults	UTI, wound infections	MRSA	Fosfomycin + Cefuzonam (dose not reported)	Minocycline + Cefuzonam (dose not reported)	5/5 (100%) vs. 4/7 (57%)	same as clinical	Poor
Guerrero, 1986 [76], Spain	Case–control study	40, adults and children	Osteomyelitis	*Staphylococcus aureus* (33), *Staphylococcus epidermidis* (4), *Escherichia coli* (2), *Enterococcus faecalis* (2), *Serratia marcescens* (2), *Mycobacterium tuberculosis* (2), *Proteus mirabilis, Citrobacter diversus, Pseudomonas fluorescens, Klebsiella oxitoca, Citrobacter freundii, P. aeruginosa* (1 each)	150–200 mg/kg/day fosfomycin[a]	150–200 mg/kg/day fosfomycin + various other antibiotics[a]	16/20 (80%) vs. 16/20 (80%)	19/20 (95%) vs. 18/20 (90%)	Poor
Corti, 2003 [21], Switzerland	Case–control study	70, children	Osteomyelitis	*Staphylococcus aureus* (12), Coagulase negative Staphylococci (6), *Streptococcus pyogenes* (2), *Streptococcus pneumoniae* (1)	200 mg/kg/day fosfomycin (mono)	Comparator 1[c]: 200 mg/kg/day fosfomycin + various combination partners Comparator 2: Various antibiotics	Only C reactive protein value given over time as measure of response. Comparable in all groups.Duration of treatment shorter in fosfomycin monotherapy ($p < 0.05$)	Not reported	poor

Abbreviations: UTI, urinary tract infections; RTI, respiratory tract infections; HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*.

[a] Resistance development of one strain was noted during treatment (fosfomycin or comparator, respectively).

[b] Resistance development of four strains were noted during fosfomycin combination therapy.

[c] Resistance development of two strains were noted during fosfomycin combination therapy.

[d] Severity of diseases was not systematically reported by the authors. Indications are presented as per definitions of the respective authors.

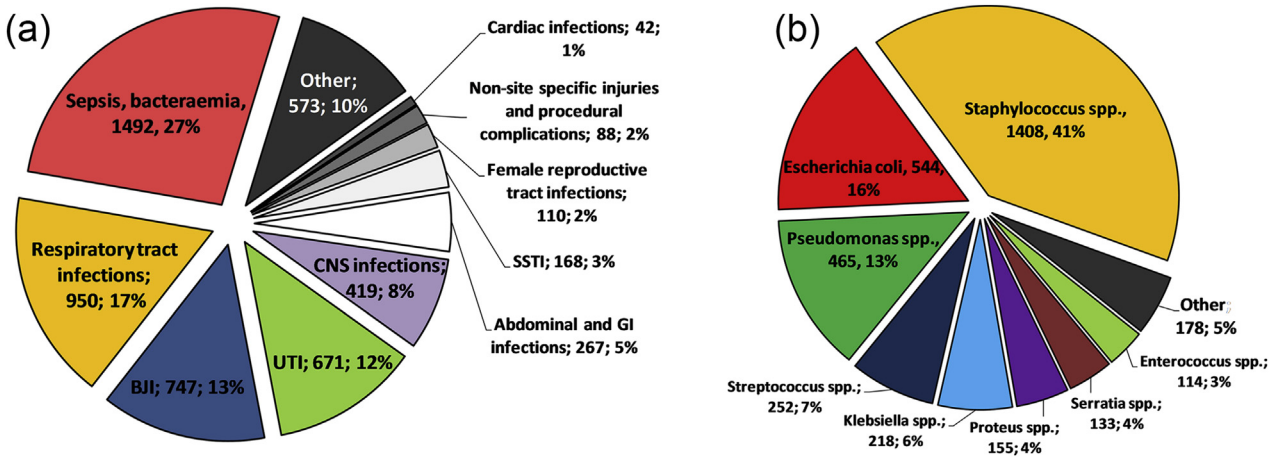

Fig. 2. Descriptive summary of the studies reviewed here. (a) Numbers of patients treated with intravenous fosfomycin by treatment indication as per MedDRA version 19.0. BJI, bone and joint infections; UTI, urinary tract infections; CNS, central nervous system infections; SSTI, skin and soft-tissue infections. (b) Absolute numbers of microbiological isolates reported by pathogen.

1.28, 95% CI 0.82–2.01). Detailed, pooled analysis based on the underlying pathogens was not possible, because most authors did not report microbiological efficacy at the individual pathogen level. However, Matsumoto et al. and Baron et al. reported on *S. aureus* (methicillin-susceptible and MRSA, respectively) indicating virtually complete eradication [73,75]. Sano et al. provided pathogen-specific data on eradication rates for *Pseudomonas* spp. (47.2%; 17/36) and *Proteus* spp. (75%; 21/28) [64]. Sirijatuphat and Thamlikitkul reported significantly higher microbiological efficacy of a combination of fosfomycin + colistin compared with colistin alone (100% versus 81.2%, p 0.01) for the eradication of carbapenem-resistant *A. baumannii* [67].

Development of resistance (monotherapy). Fifteen monotherapy studies assessed the development of resistance towards fosfomycin during monotherapy (see Supplementary material, Table S1). One study included data on patients receiving oral or parenteral fosfomycin without data stratification so was excluded from analysis [48]. The remaining studies reported different levels of emergence of resistance ranging from single isolates to 17.9% [49,57,68,88–97]. The pooled estimate for resistance development during fosfomycin monotherapy was 3.4% (95% CI 1.8%–5.1%).

Safety

Seventy-two of 128 studies (56%) reported safety data, including 480 adverse events in 2672 treated patients (18.0%; Table 2). The most common adverse events included gastrointestinal distress (nausea, vomiting, alterations of taste and diarrhoea: 140 events;

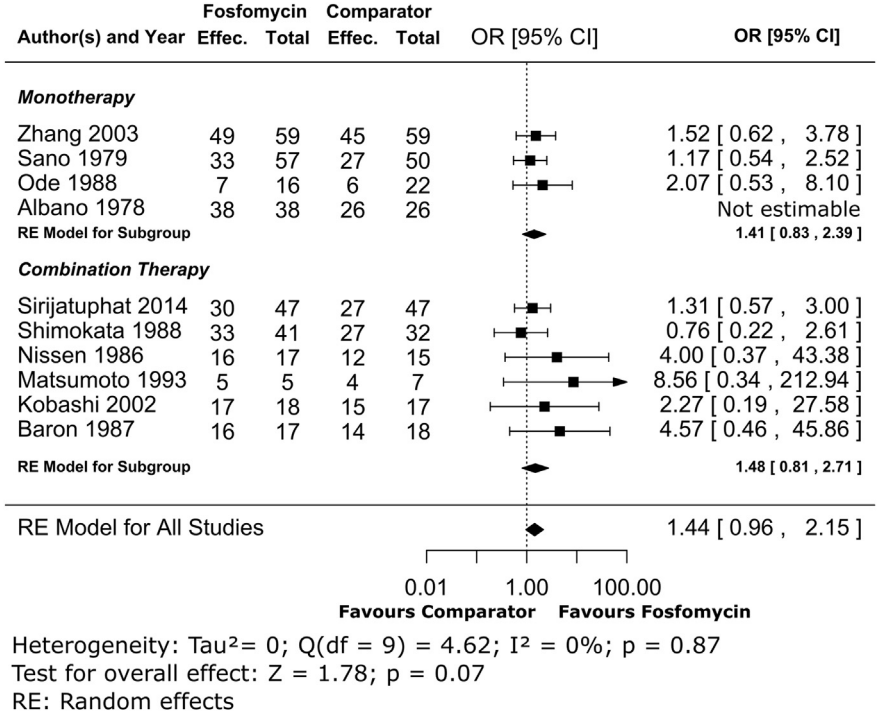

Fig. 3. Clinical efficacy in patients who were treated with intravenous fosfomycin compared with other antibiotic agents. Odds ratios (ORs) > 1 indicate increased clinical efficacy with fosfomycin. Diamonds indicate pooled ORs (± 95% CI).

Table 2
List of adverse events reported with intravenous fosfomycin use, categorized by their MedDRA preferred and high level terms

Adverse event	No. occurrence	Relative occurrence (%)
Gastrointestinal disorders	140	5.24
Gastrointestinal disorders (unspecified)	69	2.56
Diarrhoea	16	0.60
Nausea	13	0.49
Dysgeusia	31	1.16
Vomiting	9	0.34
Abdominal pain	1	0.04
Retching	1	0.04
Metabolism and nutrition disorders	99	3.71
Hypokalaemia	78	2.92
Hypernatraemia	18	0.68
Decreased appetite	1	0.04
Skin and subcutaneous tissue disorders	23	0.86
Rash	19	0.71
Rash morbilliform	2	0.07
Urticaria	1	0.04
Erythema multiforme	1	0.04
Injury, poisoning and procedural complications	27	1.01
(Thrombo)phlebitis	16	0.60
Venous intolerance	11	0.41
Altered laboratory parameters	103	3.85
Hepatic enzyme increased (unspecified)	59	2.21
Transaminases increased (unspecified)	20	0.75
Alanine aminotransferase increased	5	0.19
Laboratory test abnormal (unspecified)	5	0.19
Blood alkaline phosphatase increased	5	0.19
Aspartate aminotransferase increased	3	0.11
Blood bilirubin increased	2	0.07
Blood urea increased	2	0.07
Blood creatinine increased	1	0.04
Respiratory rate increased	1	0.04
Blood and lymphatic system disorders	19	0.71
Leukopenia*	6	0.22
Anaemia	5	0.19
Thrombocytopenia	4	0.15
Neutropenia*	3	0.11
Eosinophilia	1	0.04
General disorders and administration site conditions	19	0.71
Oedema	6	0.22
Asthenia	4	0.15
Hyperhydrosis	3	0.11
Injection site pain	3	0.11
Pyrexia	1	0.04
Nicolau syndrome*,[a]	1	0.04
Flush	1	0.04
Infections and infestations	6	0.22
Systemic candidiasis*	2	0.07
Fungal infection	2	0.07
Herpes simplex infection	2	0.07
Nervous system disorders	16	0.60
Headache	14	0.52
Vertigo	1	0.04
Hyperosmolar coma* + hyperglycaemia	1	0.04
Vascular disorders	5	0.19
Hypertension	2	0.07
Vascular pain	2	0.07
Shock*	1	0.04
Cardiac disorders	9	0.34
Tachycardia	3	0.11
Cardiac failure*,[b]	2	0.07
Pain in the heart*	2	0.07
Cardiac disorders (unspecified)	2	0.07
Other	16	0.60
Worsening of pulmonary oedema* in patients with heart insufficiency and endocarditis	2	0.07
Cough	1	0.04
Abnormal Fishberg test	1	0.04
Conjunctivitis	1	0.04
Flushing	1	0.04
Unspecified side effects	10	0.37

Relative number of occurrences is derived from the total number of studies for which adverse events have been reported (total patient number: 2672).
* Adverse events are classified as serious based on their listing on the important medical events (IME) list of the EudraVigilance Expert Working Group version 18.1.
[a] 1) Nicolau syndrome occurred in a patient which was treated with fosfomycin intramuscularly.
[b] 2) Cardiac failure was noticed in 2 patients, one 84-year old man with a pre-existing heart insufficiency, and one 75-year old women with a history of diabetes. Cardiac failure was attributed to fosfomycin, because differential diagnoses were ruled out.

5.2%) and abnormal laboratory findings (predominantly transient elevation of hepatic enzymes; 92 events; 3.4%). Hypernatraemia and/or hypokalaemia were additional relevant adverse events (86 events; 3.6%). Only 18 events (<0.01%) were classified as serious (Table 2), most commonly leukopenias (six events; <0.01%) or neutropenias (three events; <0.01%). With respect to paediatric patients, no differences were found in comparison with the overall population in relation to reported adverse events rates, indicating equally high tolerability in children.

Discussion

This systematic review reflects the clinical evidence base for intravenous fosfomycin, summarizing the available published literature, which consists of 128 studies including 5527 treated patients. The main result of this review is the finding that intravenous fosfomycin did not show a different level of clinical or microbiological efficacy compared with other antibiotics against which it was tested in comparative trials (primary outcome: OR). Despite various different comparators (penicillins, cephalosporins and aminoglycosides), indications and treatment regimens (monotherapy/combination therapy), pooled results were robust with no indication of heterogeneity or sensitivity towards study quality. With respect to microbiological efficacy, data stratified by the causing pathogens was very scarce. Those studies providing species-specific data indicated excellent efficacy against *S. aureus*, even in monotherapy, reaffirming the traditional perception of fosfomycin as an anti-staphylococcal drug. High efficacy against *A. baumannii* was noted in combination with colistin, despite the intrinsically low activity of fosfomycin against this pathogen. The added effect can be explained by synergistic activity between fosfomycin and colistin [98]. Microbiological efficacy against *Pseudomonas aeruginosa* in monotherapy seemed rather limited [64], consistent with EUCAST guidance suggesting that combination with other antibiotics is required for this pathogen [99]. Fosfomycin was a well-tolerated drug, showing a favourable safety profile with serious adverse events being reported very infrequently. Adverse events were generally mild and did not require discontinuation of treatment. However, physicians should be aware of the risks of hypernatraemia and/or hypokalaemia representing important side effects requiring monitoring.

Our review additionally assessed fosfomycin's clinical usage patterns: it is predominantly used in complex infections such as sepsis/bacteraemia and respiratory, urinary tract, CNS, as well as bone and joint infections. During its development period,

fosfomycin was primarily regarded as an anti-staphylococcal agent, but more recent reports use it more often against MDR Gram-negative species. This additional usage pattern reflects the rising rates of bacterial resistance to anti-infective drugs worldwide and is concordant with the consistently low antimicrobial resistance rates for fosfomycin [5]. In addition to the targeted pathogens, therapy schemes of intravenous fosfomycin have also dramatically changed, resulting in a switch from monotherapy to combination therapy. The present review shows that resistance emerged during fosfomycin monotherapy at rates ranging from <3% to 17.9% (pooled estimate 3.4%). This matches the rates reported for other antibiotic classes (i.e. penicillins, aminoglycosides or carbapenems) [100,101] as well as those reported by other authors for fosfomycin [102]. Our results confirm the generally noted discrepancy between high rates of *in vitro* emergence of resistance and its evidently low clinical relevance [102].

Limitations of our analysis are mostly inherent to the studies included in the review, i.e. lack of appropriately statistically powered, prospectively collected, or comparative trials. Half of the few randomized controlled trials included in our analysis (four of eight) did not reflect current intravenous fosfomycin dosing schemes and all lacked the statistical power of classical pivotal trials. Most of the available data still come from retrospective case series, with the corresponding intrinsic risk of bias. Heterogeneity of studies and reporting quality restricted the possible options for data stratification. A risk of bias, particularly selection bias, may therefore remain. Efficacy endpoints (clinical and microbiological) were applied using the definitions given in the respective studies and not adjusted by the authors for potential confounders. The strength of evidence presented in this review is consequently limited as well. However, the limitations discussed have to be seen in the context of the available data and the reporting standards decades ago. The data presented in this review are therefore expected to provide an accurate reflection of the past and current clinical use of intravenous fosfomycin and the current clinical evidence.

Conclusions and future outlook

The data presented here lead to the conclusion that fosfomycin has comparable clinical efficacy with other antibiotic classes and has retained activity against MDR organisms. Fosfomycin therefore has a place in the armamentarium of substances to combat challenging indications in the multidrug resistance era. Moreover, it shows an overall favourable safety profile. Sepsis/bacteraemia, and respiratory tract, urinary tract, CNS, and bone and joint infections were identified as the most important indications, combined with a more recent trend towards the treatment of MDR Gram-negative bacteria. Well-designed randomized controlled trials comparing intravenous fosfomycin therapy with state-of-the-art first-line therapy alternatives are desired to confirm the currently available clinical evidence. Ongoing studies with fosfomycin in monotherapy and combination therapy are addressing these questions with respect to complicated or bacteraemic UTI and MRSA bacteraemia [103,104]. Respiratory tract, CNS, and bone and joint infections are identified as additional areas in which new studies of intravenous fosfomycin may fill gaps in clinical research.

Transparency declaration

BG reports personal fees from Infectopharm, outside the submitted work; WG reports personal fees from Infectopharm, Sandoz and DiaSorin, outside the submitted work; RB reports personal fees from AstraZeneca, Merck, Achaogen and Infectopharm, outside the submitted work; AD reports personal fees from MSF France, Sanofi, Infectopharm, Astellas and Novartis, outside the submitted work; and DBL is employed by Infectopharm.

Acknowledgements

All authors approved the final version of the manuscript. JRB receives funding for research from the Ministerio de Economía y Competitividad, Instituto de Salud Carlos III—co-financed by European Development Regional Fund “A way to achieve Europe” ERDF, Spanish Network for the Research in Infectious Diseases (REIPI RD12/0015), FIS (PI 13/01282), and the Innovative Medicines Initiative (European Union and EFPIA partners in kind; agreements 115523 COMBACTE-NET, 115620 COMBACTE-CARE and 115737 COMBACTE-MAGNET projects).

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.cmi.2016.12.005.

References

[1] Kahan FM, Kahan JS, Cassidy PJ, Kropp H. The mechanism of action of fosfomycin (phosphonomycin). Ann N Y Acad Sci 1974;235:364–86.
[2] Paul-Ehrlich-Gesellschaft für Chemotherapie. Resistenzstudie 2013. Abschlussbericht Teilprojekt H - Epidemiologie und Resistenzsituation bei klinisch wichtigen Infektionserregern aus dem Hospitalbereich gegenüber Antibiotika. 2015. Available at: http://www.p-e-g.org/econtext/Berichte%20der%20Studien/.
[3] Allerberger F, Klare I. In-vitro activity of fosfomycin against vancomycin-resistant enterococci. J Antimicrob Chemother 1999;43:211–7.
[4] Maraki S, Samonis G, Rafailidis PI, Vouloumanou EK, Mavromanolakis E, Falagas ME. Susceptibility of urinary tract bacteria to fosfomycin. Antimicrob Agents Chemother 2009;53:4508–10.
[5] Falagas ME, Kastoris AC, Kapaskelis AM, Karageorgopoulos DE. Fosfomycin for the treatment of multidrug-resistant, including extended-spectrum β-lactamase producing, Enterobacteriaceae infections: a systematic review. Lancet Infect Dis 2010;10:43–50.
[6] Boyanova L. Susceptibility of anaerobes to fusidic acid and fosfomycin. Int J Antimicrob Agents 2015;45:560–1.
[7] 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.
[8] 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.
[9] Kuhnen E, Pfeifer G, Frenkel C. Penetration of fosfomycin into cerebrospinal fluid across non-inflamed and inflamed meninges. Infection 1987;15:422–4.
[10] 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 Antimocrob Chemother 2009;64:574–8.
[11] 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.
[12] Legat FJ, Maier A, Dittrich P, Zenahlik P, Kern T, Nuhsbaumer S, et al. Penetration of fosfomycin into inflammatory lesions in patients wich cellulitis or diabetic foot syndrome. Antimicrob Agents Chemother 2003;47:371–4.
[13] Parker SL, Frantzeskaki F, Wallis SC, Diakaki C, Giamarellou H, Koulenti D, et al. Population pharmacokinetics of fosfomycin in critically ill patients. Antimicrob Agents Chemother 2015;59:6471–6.
[14] del Río A, Gasch O, Moreno A, Peña C, Cuquet J, Soy D, et al. Efficacy and safety of fosfomycin plus imipenem as rescue therapy for complicated bacteremia and endocarditis due to methicillin-resistant *Staphylococcus aureus*: a multicenter clinical trial. Clin Infect Dis 2014;59:1105–12.
[15] Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Software 2010;36:1–48.
[16] Aidan P, Francois M, Prunel M, Narcy P. Cellulite de la région orbitaire chez l'enfant. Arch Pediatr 1994;1:879–85.
[17] Badelon O, Bingen E, Sauzeau C, Lambert-Zechovsky N, de Ribier A, Bensahel H. [Choice of first-line antibiotic therapy in the treatment of bone and joint infections in children]. Pathol Biol (Paris) 1988;36:746–9.
[18] Bode U. Infektionen in der Pädiatrischen Onkologie. In: Adam D, editor. Fosfomycin – Berichtsband zum Workshop Aktuelle Aspekte in der Infektionstherapie. Frankfurt/Main: pmi; 1986. p. 19–23.

[19] Cedrato AE, Martinez Meyer CA, Koltan A, Touceda C, Del Boca JC, Galan H, et al. Fosfomicina sola o asociada a otros antibioticos. Revissa Argentina de Pediatria 1977;3(6).

[20] Chung SS, Iazzetti AV, Nobrega FJ, Farhat CK. Septicemia neonatal—consideracoes etiopatogenicas terapeuticas. J pediat (Rio de J) 1979;46(3).

[21] Corti N, Sennhauser FH, Stauffer UG, Nadal D. Fosfomycin for the initial treatment of acute haematogenous osteomyelitis. Arch Dis Child 2003;88:512–6.

[22] Fitoussi F, Litzelmann E, Ilharreborde B, Morel E, Mazda K, Pennecot GF. Hematogenous osteomyelitis of the wrist in children. J Pediatr Orthop 2007;27:810–3.

[23] François M, Mariani-Kurkdjian P, Dupont E, Bingen E. Acute ethmoiditis in children, a series of 125 cases. Arch pediatr 2006;13:6–10.

[24] François M, Mariani-Kurkdjian P, Elbakkouri W, Bingen E. [Suppurative cervical lymphadenitis in children. Review of 45 patients]. Ann Otolaryngol Chir Cervicofac 2004;121:110–4.

[25] Gouyon JB, Francois C, Semama D, Sandre D, Duez JM, Portier H. Septicemies nosocomiales a staphylocoques epidermidis et aures chez le nouveauné. Ann Pediatr Paris 1990;37:21–5.

[26] Gouyon JB, Duez JM, Portier H, Brichon P, Kohli E, Alison M. L'association fosfomycine-céfotaxime dans les infections sévères staphylococciques du nouveau-né. La Presse Méd 1985;14:2135–8.

[27] Guggenbichler JP, Bonatti H, Rottensteiner F. Resistenz der Staphylokokken gegen intrazelluläre Abtötung durch Makrophagen – ein neuses pathophysiologisches Konzept der akuten hämatogenen Osteomyelitis im Kindesalter und seine therapeutischen Konsequenzen. Pädiatrie und Pädologie 1989;24:21–32.

[28] Guggenbichler JP, Frisch J. Fosfomycin in der Behandlung der eitrigen Meningitis im Früh- und Neugeborenenalter. In: Spitzy KH, Adam D, editors. Fosfomycin – ein neuartiges Antibiotikum, Internationales Symposiums Salzburg 1982. Frankfurt/Zürich: pmi; 1983. p. 169–76.

[29] Guibert M, Magny JF, Poudenx F, Lebrun L, Dehan M. [Comparative pharmacokinetics of fosfomycin in the neonate: 2 modes of administration]. Pathol Biol (Paris) 1987;35:750–2.

[30] Hepping N, Bode U, Fleischhack G, Wiszniewsky G, Molitor E, Simon A. Fosfomycin: prospektive Analyse von 100 Behandlungskursen in einem pädiatrisch onkologischen Zentrum. Chemother J 2008;17:25–8.

[31] Hori M, Kono S, Joh K. Clinical experiences of fosfomycin (FOM) for intravenous injection against severe infantile acute bacterial infections. Chemotherapy (Jpn) 1975;23:3409–14.

[32] Klumpp H, Engert J, Körling W. Behandlungsmöglichkeiten bei Ventilsepsis. In: Knothe H, editor. Fosfomycin. Berichtsband zum Workshop Pädiatrie. Frankfurt/Zürich: pmi; 1985. p. 46–52.

[33] Lagier P, Perraud-Bimar P, Dejode JM, Brun T, Bimar J. Expérience de la fosfomycine dans le traitement des infections sévères en réanimation pédiatrique. Ann Pédiatr (Paris) 1987;34:457–61.

[34] Llorens J, Ley G, Fores A, Olay T. Acute infantile pneumonopathies treated with fosfomycin. Chemotherapy 1977;23(Suppl 1):315–23.

[35] Marget W, Lohse K. Fosfomycin in the treatment of infections difficult to treat. In: Fosfomycin. Proceedings of the International Symposium. March 1986 Mexico. Madrid: Instituto de Farmacologia Espanõla (CEPA); 1987. p. 229–31.

[36] Panico Grecco S, de Sicca Filho FA, Boucas MEA. Fosfomicina como terapeutica antiinfecciosa em pediatria. A Folha Medica 1978;77(3).

[37] Pillwein K, Guggenbichler P, Konzert W. Fosfomycin in der Behandlung der akuten hämatogenen Osteomyelitis im Säuglingsalter. In: Spitzy KH, Adam D, editors. Fosfomycin - ein neuartiges Antibiotikum, Internationales Symposiums Salzburg 1982. Frankfurt/Zürich: pmi; 1983. p. 181–95.

[38] Reinehr T, Bürk G, Michel E, Andler W. Chronic osteomyelitis in childhood: is surgery always indicated? Infection 2000;28:282–6.

[39] Riedl M, Allerberger F, Guggenbichler JP, Semenitz E, Dierich MP. Behandlung von Sepsiserkrankungen im Kindesalter mit zeitlich versetzter Gabe von Antibiotika-Kombinationen. Wien Medizin Wochenschr 1991;141:172–6.

[40] Roche G, Bollaert PE, Gerard A, Canton Ph, Weber M, Czorny A, et al. Infections a cocci Gram positif au cours des dérivations de L.C.R. Traitment par l'association Fosfomycine-Oxacilline. Med Maladies Infect 1983;13:426–7.

[41] Rossignol S, Regnier C. La fosfomycine dans les infections sévères en nèonatologie. Ann Pédiat (Paris) 1984;31:437–44.

[42] Sawada S. [Clinical experience with fosfomycin for intravenous use in respiratory infections]. Chemotherapy (Jpn) 1975;23:3406–8.

[43] Baquero F, Hortelano JG, Navarro M, Scarpellini A, Jara P, Cañedo T, et al. Antibiotherapy of *Serratia marcescens* septicemia in children. Chemotherapy 1977;23(Suppl 1):416–22.

[44] Dinh A, Salomon J, Bru JP, Bernard L. Fosfomycin: efficacy against infections caused by multidrug-resistant bacteria. Scand J Infect Dis 2012;44:182–9.

[45] Boulard G, Quentin C, Scontrini G, Dautheribes M, Pouguet P, Sabathie M. Traitement des ventriculites a *Staphylococcus epidermidis* sur materiel par l'association fosfomycine-aminoside. Evolution des taux ventriculaires de fosfomycine. Pathol Biol Paris 1983;31:525–7.

[46] Dureux JB, Voiriot P, Gerard A, Maillard S, Tronel H, Canton P. Expérience de la fosfomycine dans le traitement des septicémies à staphylocoque. Sem Hop Paris 1987;63:3556–8.

[47] Fleurette J, Estanove S, Brun Y, Meyer P, Reverdy ME, Ros A, et al. Interet de la fosfomycine en association dans le traitement des infections graves. Lyon Med 1980;244:191–5.

[48] Gobernado M, Santos M, Paz M, Roman J, Masceros E. Five years' experience with fosfomycin in a Spanish hospital. Bacteriological and clinical results. In: Siegenthaler W, Lüthy R, editors. Current Chemotherapy. Proceedings of the 10th International Congress on Chemotherapy. Zurich/Swizerland; 1978. p. 677–9.

[49] Hernandesz-Casado V. Fosfomycin in a traumatological department. Chemotherapy 1977;23(Suppl 1):403–10.

[50] Itami Y, Kobayakawa H, Ohto T, Yoshida M, Ueno H, Nishikawa M, et al. [Basic and clinical studies on fosfomycin in orthopedic field]. Chemotherapy (Jpn) 1975;23:3686–93.

[51] 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;35:839–42.

[52] Pardo Zubiris A, Gimeno Blasco L, Andonegui Oteiza J. Evaluation of Fosfomycin in an Intensive Care Unit. Chemotherapy 1977;23(Suppl 1):411–5.

[53] Perea EJ, Damaso D, Moreno-Lopes M, Rodriguez A. Infecciones diversas tratadas con fosfomicina. Progr terapéut clín 1974;27:1–15.

[54] Portier H, Tremeaux JC, Chavanet P, Gouyon JB, Duez JM, Kazmierczak A. Treatment of severe staphylococcal infections with cefotaxime and fosfomycin in combination. J Antimicrob Chemother 1984;14(Suppl B):277–84.

[55] Ruiz Moyano J, Sicilia T. Fosfomicina en meningitis neumococica. Inmunologika 1981;2(Suppl. 1):84–6.

[56] Sicilia T, Estevez E, Rodriguez A. Fosfomycin penetration into the cerebrospinal fluid of patients with bacterial meningitis. Chemotherapy 1981;27:405–13.

[57] Stammberger H. [Fosfomycin – a new antibiotic in rhinootolaryngology]. HNO 1983;31:436–9.

[58] Yano T, Hara H, Goto T. Therapeutic experience of intravenous fosfomycin (Fom-Na) in orthopedical field. Chemotherapy (Jpn) 1975;23:3525–7.

[59] Misawa S, Tsuda S, Taniwaki M, Horiike S, Ariyama Y, Hirakawa K, et al. [A combined consecutive therapy with fosfomycin and sulbactam/cefoperazone for bacterial infections associated with hematological diseases]. Jpn J Antibiot 1995;48:514–21.

[60] Tsuda S, Kuzuyama Y, Nakai H, Seriu T, Takashima T, Tanaka S, et al. [Clinical evaluation of imipenem/cilastatin sodium and fosfomycin as second-line combination chemotherapy in severe infections associated with hematologic disorders]. Jpn J Antibiot 1993;46:171–83.

[61] Hiraoka A, Hasegawa H, Horiuchi A, Masaoka T. [Combination effect of fosfomycin and sulbactam/cefoperazone for opportunistic infections in patients with hematological disorders: a randomised crossover trial of sequential administration]. Blood 1996;88(Suppl. Pt 1).

[62] Kitamura K, Hirai H, Hosoya N, Sugai M, Karasawa M, Naruse T, et al. [Clinical efficacy of fosfomycin in combination with sulbactam/cefoperazone in the treatment of severe infections complicated to blood dyscrasia. Working Group of Kanto Combination Therapy for FOM + SBT/CPZ]. Kansenshogaku Zasshi 1998;72:761–70.

[63] Hirakawa K, Tsuda S, Misawa S, Ueda Y, Kaneko H, Nakao M, et al. [Clinical effects of a combination treatment with fosfomycin and clavulanic acid/ticarcillin for infections in patients complicated with hematological disorders]. Jpn J Antibiot 1994;47:521–9.

[64] Sano S, Karino K, Nakano K, Watanabe T, Masahiro H. [Comparative study of the efficacy on fosfomycin Na and sulbenicilin Na against the chronic urinary tract infections by *Pseudomonas aeruginosa* and *Proteus vulgaris*]. Acta Urol Jpn 1979;25(1).

[65] Kobashi Y, Ohba H, Okimoto N, Tada A, Kawahara S, Ishida T, et al. Clinical analysis of combined consecutive therapy with fosfomycin and sulbactam/cefoperazone for patients with pneumonia. Jpn J Chemother 2002;50:429–34.

[66] Shimokata K, Torigai K, Kato M, Sakai S, Nomura F, Ito T, et al. [Effects of cefotaxime single administration and of cefotaxime + fosfomycin administration against respiratory tract infections]. Jpn J Antibiot 1988;41:1261–71.

[67] Sirijatuphat R, Thamlikitkul V. Preliminary study of colistin versus colistin plus fosfomycin for treatment of carbapenem-resistant *Acinetobacter baumannii* infections. Antimicrob Agents Chemother 2014;58:5598–601.

[68] Ode B, Haidl S, Hoffstedt B, Walder M, Ursing J. Fosfomycin versus ampicillin in the treatment of acute pyelonephritis. Chemioterapia 1988;7:96–100.

[69] 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.

[70] Zhang JJ. [Observations on the effect of sodium fosfomycin on the lower respiratory tract infection]. Chin J Antibiotics 2003;28:361–3.

[71] Otsuka M, Sawahata T, Nakai T, Hasegawa S, Iwata S, Yoshizawa Y, et al. [Efficacy of combination therapy against MRSA in Ibaraki Prefecture]. Jpn J Antibiot 1994;47:781–9.

[72] Albano V, Giambanco V, Alio L. Note cliniche sull'impiego della fosfomicina in ostetricia e ginecologia. Boil Chim Farm 1978;117:428–31.

[73] Baron D, Touze MD, Tasseau F, Reynaud A, Derriennic M, Courtieu AL. Comparaison entre fosfomycine-pénicilline M et pénicilline M-Gentamicine. A propos de 35 infections sévères à *Staphylococcus aureus* méticilline-sensibles. Rev Méd interne 1987;8:109–14.

[74] Apisarnthanarak A, Mundy LM. Carbapenem-resistant *Pseudomonas aeruginosa* pneumonia with intermediate minimum inhibitory concentrations to doripenem: combination therapy with high-dose, 4-h infusion of doripenem

plus fosfomycin versus intravenous colistin plus fosfomycin. Int J Antimicrob Agents 2012;39:271–2.
[75] Matsumoto T, Kubo S, Haraoka M, Takahashi K, Tanaka M, Sakumoto M, et al. Combination chemotherapy for infections due to methicillin-resistant *Staphylococcus aureus* with combination therapy by cefuzonam and fosfomycin or minocycline in the urologic field. Clin Ther 1993;15:819–28.
[76] Guerrero A, Diaz-Peletier R, Hellin T. Fosfomycin in the treatment of osteomyelitis. In: Fosfomycin. Proceedings of the International Symposium. March 1986 Mexico. Madrid: Instituto de Farmacologia Espanõla (CEPA); 1987. p. 136–44.
[77] Baron D, Desjars P, Touze MD, Tasseau F, Potel G. Clinical Study on combined therapy with fosfomycin for staphylococcal infections. In: Fosfomycin. Proceedings of the International Symposium. March 1986 Mexico. Madrid: Instituto de Farmacologia Espanõla (CEPA); 1987. p. 172–87.
[78] Baron D, Drugeon H. Septicemias e infecciones óseas por *Staphylococcus aureus* resistentes a la meticilina y a los aminoglucósidos. Tratamiento con fosfomicina-oxacilina. Inmunologika. Edición especial: 3rd international symposium on Fosfomycin on the occasion of the 25th Anniversary of 1st Research Center Instituto de Farmacología Espanola. 1981. p. 80–3.
[79] Baron D, Drugeon HB, Touze MD, Derrienic M, Tasseau F, Reynaud A. Les infections a staphylocoques meticilline-resistants. In: Pocidalo JJ, Vachon F, editors. Problèmes actuels de pathologie infectieuse et de réanimation. Paris: Arnette; 1984. p. 1–24.
[80] Kono K, Takeda S, Tatara I, Arakawa K, Tanaka H, Miyake S, et al. Combined therapy with arbekacin and fosfomycin for methicillin-resistant *Staphylococcus aureus* infections. Jpn J Antibiotics 1994;47:798–803.
[81] Lau WY, Teoh-Chan CH, Fan ST, Lau KF. In vitro and in vivo study of fosfomycin in methicillin-resistant *Staphylococcus aureus* septicaemia. J Hyg Camb 1986;96:419–32.
[82] May T, Janbon F, Beuscart C, Meyran M, Roue R. [Severe infections caused by methicillin-resistant *Staphylococcus aureus*. 62 cases]. Presse Med 1993;22:909–13.
[83] Apisarnthanarak A, Mundy LM. Use of high-dose 4-hour infusion of doripenem, in combination with fosfomycin, for treatment of carbapenem-resistant *Pseudomonas aeruginosa* pneumonia. Clin Infect Dis 2010;51:1351–2.
[84] Michalopoulos A, Virtzili S, Rafailidis P, Chalevelakis G, Damala M, Falagas ME. Intravenous fosfomycin for the treatment of nosocomial infections caused by carbapenem-resistant *Klebsiella pneumoniae* in critically ill patients: a prospective evaluation. Clin Microbiol Infect 2010;16:184–6.
[85] Pontikis K, Karaiskos I, Bastani S, Dimopoulos G, Kalogirou M, Katsiari M, et al. Outcomes of critically ill intensive care unit patients treated with fosfomycin for infections due to pandrug-resistant and extensively drug-resistant carbapenemase-producing Gram-negative bacteria. International J Antimicrob Agents 2014;43:52–9.
[86] Stöckl B, Schmutzhard E. Antimikrobielle Therapie der Spondylodiszitis – Überlegungen zur Optimierung. Chemother J 2005;14:11–5.
[87] Stengel D, Görzer E, Schintler M, Legat FJ, Amann W, Pieber T, et al. Second-line treatment of limb-threatening diabetic foot infections with intravenous fosfomycin. J Chemother 2005;17:527–35.
[88] Timmler R, Sauer W. Klinische Prüfung BM 04.005 (Fosfomycin). Abschlussbericht für die 4-Gramm-Tagesdosis. Klinische Entwicklung Abteilung Chemotherapie. Boehringer Mannheim GmbH; 1978.
[89] Timmler R, Sauer W. Klinische Prüfung BM 04.005 (Fosfomycin). Abschlussbericht für die 6-Gramm-Tagesdosis. Klinische Entwicklung Abteilung Chemotherapie. Boehringer Mannheim GmbH; 1978.
[90] Quentin C, Boulard G, Bebear C, Sabathie M. Ventricular fluid concentration of fosfomycin in patients with ventriculitis. In: Brumfitt W, Finland M, editors. Proceedings of the 13th International Congress of Chemotherapy. Viena: H. Egermann; 1983. p. 8–12. SS 4.6/8 part 37.
[91] Meissner A, Haag R, Rahmanzadeh R. Adjuvant fosfomycin medication in chronic osteomyelitis. Infection 1989;17:146–51.
[92] Naber KG, Timmler R. Keimelimination durch Fosfomycin bei komplizierten Harnwegsinfektionen. Therapiewoche 1983;33:3300–6.
[93] Gudin J, Santos M, Ruano M, Rafecas J, Gobernado M. Fosfomycin in the treatment of septicemia. In: Fosfomycin. Proceedings of the International Symposium. March 1986 Mexico. Madrid: Instituto de Farmacologia Espanõla (CEPA); 1987. p. 166–71.
[94] Bertoye A, Vincent P, Fournier G, Marcel JP, Olivier G, Fournier G. Traitement par la fosfomycine des infections severes observees en service de reanimation. Lyon Med 1980;243:177–82.
[95] Federspil P, Schätzle W, Schedler M. Wirksamkeit, Nebenwirkungen und Pharmakokinetik von Fosfomycin bei Hals-Nasen-Ohren-Infektionen. Therapiewoche 1983;33:4372–82.
[96] Peters HJ, Eicher R. Klinische Erfahrungen mit Fosfomycin bei Harnwegsinfektionen. MMW Munch Med Wochenschr 1981;123:748–50.
[97] Peters HJ, Eicher R. Fosfomycin, klinische Wirksamkeit und Verträglichkeit bei Harnwegsinfektionen. Klinikarzt 1982;11:168–80.
[98] Santimaleeworagun W, Wongpoowarak P, Chayakul P, Pattharachayakul S, Tansakul P, Garey KW. In vitro activity of colistin or sulbactam in combination with fosfomycin or imipenem against clinical isolates of carbapenem-resistant *Acinetobacter baumannii* producing OXA-23 carbapenemases. Southeast Asian J Trop Med Public Health 2011;42:890–900.
[99] The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 6.0. 2016. Available at:, http://www.eucast.org.
[100] Milatovic D, Braveny I. Development of resistance during antibiotic therapy. Eur J Clin Microbiol 1987;6:234–44.
[101] Fish DN, Piscitelli SC, Danzinger LH. Development of resistance during antimicrobial therapy: a review of antibiotic classes and patient characteristics in 173 studies. Pharmacotherapy 1995;15:279–91.
[102] Karageorgopoulos DE, Wang R, Yu XH, Falagas ME. Fosfomycin: evaluation of the published evidence on the emergence of antimicrobial resistance in Gram-negative pathogens. J Antimicrob Chemother 2012;67:255–68.
[103] Rosso-Fernández C, Sojo-Dorado J, Barriga A, Lavín-Alconero L, Palacios Z, López-Hernández I, et al. Fosfomycin versus meropenem in bacteraemic urinary tract infections caused by extended-spectrum β-lactamase-producing *Escherichia coli* (FOREST): study protocol for an investigator-driven randomised controlled trial. BMJ Open 2015;5:e007363.
[104] Shaw E, Miró JM, Puig-Asensio M, Pigrau C, Barcenilla F, Murillas J, et al. Daptomycin plus fosfomycin versus daptomycin monotherapy in treating MRSA: protocol of a multicentre, randomised, phase III trial. BMJ Open 2015;5(3):e006723.