Intravenous fosfomycin – Back to the future. Systematic review and meta-analysis of the clinical literature

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PII: S1198-743X(16)30610-3
DOI: 10.1016/j.cmi.2016.12.005
Reference: CMI 794

To appear in: Clinical Microbiology and Infection

Received Date: 24 August 2016
Revised Date: 12 November 2016
Accepted Date: 3 December 2016


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Title: Intravenous fosfomycin – Back to the future. Systematic review and meta-analysis of the clinical literature

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Manuscript category: Systematic review

Keywords: Fosfomycin, intravenous, systematic review, meta-analysis, clinical outcome, multi drug resistance (MDR)
ABSTRACT (242 words)

Objectives: We conducted a systematic review and meta-analysis to summarise 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 randomised controlled and comparative observational studies were synthesized using meta-analysis to calculate pooled effect sizes. Results: 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 efficacy (OR: 1.28, [95% CI: 0.82–2.01]) 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 mono and combination therapy, whereas studies from 1990 on focused on combination therapy (fosfomycin + β-lactams or aminoglycosides) for challenging infections frequently caused by MDROs. Conclusion: Intravenous fosfomycin can play a vital role in the antibiotic armamentarium, given its long history of effective and safe use. However, well-designed randomised controlled trials are still desired.
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 has initially been registered in various European (Spain, Germany, France) and non-European (Japan) countries. The clinical use of intravenous fosfomycin has remained at quite constant but low levels. Interest in intravenous fosfomycin has renewed in the 21st 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 negative species, but shows only very limited activity against anaerobic species, most importantly Bacteroides as well as against selected Gram-negative species such as *A. baumannii* or *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 (BJI) (10), the 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 summarise 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 fosfomycin (i.v.) use and help 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 Data. Additionally, we identified records by a hand search of local journals not indexed in 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, intraabdominal 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), mono- or combination therapy (at least one 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 (randomised controlled and comparative observational) 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](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 randomisation, 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, pre-specified 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), poor-fair (5), fair (6-8), fair-good (9) 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 effect model) of clinical and microbiological efficacy using odds ratios (OR) as the effect size estimate. ORs > 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 vs.
trials with poor-quality excluded. Additionally, an exploratory analysis was conducted to explore associations of covariates with clinical efficacy (see Supplementary Data).

All analyses were carried out in the statistical software R 3.3.1. The “metafor” package was used to run meta-analyses and -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 (IME) list version 18.1.

RESULTS

Out 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 data 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. 28/128 studies (21.9%) exclusively reported on paediatric populations (n = 819) (18-45). 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 (46-60). Seven studies focused on the use of fosfomycin in patients with haematological malignancies (61-67).
Quality of studies

Almost half of the reports (61/128; 48%) were retrospective case series and only a minority of studies were comparative (6 non-randomised controlled trials and 3 case-control studies; 9/128; 7%) or randomised 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 Supplementary Data for individual scores). Most studies lacked statistical power, randomisation or blinding procedures, adequate description of randomisation 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, BJI (mostly osteomyelitis) and CNS infections (see 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 methicillin-resistant *S. aureus* (MRSA) or *S. epidermidis* (MRSE) (68-75) or carbapenem-resistant and MDR Gram-negative species (resistance status reported as defined by the respective authors) (46, 76-80).

Studies on MDR Gram-negative species were all published after 2010.
Dosing and therapy regimes

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 2-3 equal doses. In contrast, dosing was drastically 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 (34, 79, 22) (82, 59, 83). 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 (Fig. S-1). 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 (7 randomised) 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 mono- (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 6 studies with fair or good study quality, fosfomycin combination therapy was used against RTIs/pneumonias (3/3 studies). Monotherapy was used against UTIs (2/3 studies), or RTIs (1/3 study). No heterogeneity was observed in all meta-analyses.

**Microbiology**

**Microbiological efficacy**

The study of Albano et al. (109) did not report any microbiological efficacy data and was thus excluded. Pooled analysis of the remaining 9 comparative studies did not indicate any difference between fosfomycin and its comparators (OR: 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, Baron et al. and Matsumoto et al. reported on *S. aureus* (MRSA and MSSA, respectively) indicating virtually complete eradication (110, 74). Sano et al. provided pathogen-specific data on eradication rates for *Pseudomonas* spp. (47.2%; 17/36) and *Proteus* spp. (75%; 21/28) (103). The group of Sirijatuphat reported significantly higher microbiological efficacy of a combination of fosfomycin + colistin compared to colistin alone (100% vs. 81.2%, p = 0.01) for the eradication of carbapenem-resistant *A. baumannii* (80).

**Development of resistance (monotherapy)**

Fifteen monotherapy studies assessed the development of resistance towards fosfomycin during monotherapy (Table S-3). One study (97) included data on patients receiving oral or parenteral fosfomycin without data stratification and was thus excluded from analysis. The remaining studies reported different levels of emergence of resistance ranging from single isolates to 17.9% (16, 17, 59, 51, 88-96). 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 (AEs) in 2672 treated patients (18.0%; Table 2). The most common AEs included gastrointestinal distress (nausea, vomiting, alterations of taste and diarrhoea: 140 events; 5.2%) and abnormal laboratory findings (predominantly transient elevation of hepatic enzymes; 92 events; 3.4%). Hypernatraemia and/or hypokalaemia were additional relevant AEs (86 events; 3.6%). Only 18 events (<0.01%) were classified as serious (Table 2), most commonly leukopenias (6 events; <0.01%) or neutropenias (3 events; <0.01%). With respect to paediatric patients, no differences were found in comparison with the overall population in relation to reported AE rates, indicating equally high tolerability in children.

DISCUSSION

This systematic review reflects the clinical evidence base for intravenous fosfomycin, summarising 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 to 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 (mono/combination), 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 scare. 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 (85). Microbiological efficacy against \textit{P. aeruginosa} in monotherapy seemed rather limited (103), consistent with EUCAST guidance suggesting that combination with other antibiotics is required for this pathogen (86). Fosfomycin was a well-tolerated drug, showing a favourable safety profile with serious adverse events being reported very infrequently. AEs 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 fosfomycin (i.v.) have also dramatically changed resulting in a switch from mono- 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) (98, 99) as well as those reported by other authors for fosfomycin (87). Our results confirm the generally noted discrepancy between high rates of \textit{in vitro} emergence of resistance and its evidently low clinical relevance (87).
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. More than half of the few RCTs included in our analysis (4/8) did not reflect current intravenous fosfomycin dosing schemes and all lacked the statistical power of classical pivotal trials. Most of the available data still comes 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 thus 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 thus 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 MDROs. 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 RCTs comparing intravenous fosfomycin therapy with state-of-the-art first-line therapy alternatives are desired in order to confirm the currently available clinical evidence. Ongoing studies with fosfomycin in mono and combination therapy are
addressing these questions with respect to complicated or bacteraemic UTI and MRSA bacteraemia (101, 102). 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.

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).

TRANSPARENCY DECLARATION

Dr. Grabein reports personal fees from Infectopharm, outside the submitted work; Dr. Graninger reports personal fees from Infectopharm, Sandoz and DiaSorin, outside the submitted work; Dr. Rodríguez Baño reports personal fees from AstraZeneca, Merck, Achaogen and Infectopharm, outside the submitted work; Dr. Dinh reports personal fees from MSF France, Sanofi, Infectopharm, Astellas and Novartis, outside the submitted work; Dr. Liesenfeld is employed by Infectopharm.
REFERENCES


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533
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FIGURE CAPTIONS

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

**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.

**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).
### TABLES

**Table 1.** Summary of studies comparing intravenous fosfomycin therapy (either mono or combination) against another therapy regime.

<table>
<thead>
<tr>
<th>Author, yr, country</th>
<th>Design</th>
<th>Patients, n</th>
<th>Infection</th>
<th>Isolated pathogens</th>
<th>Fosfomycin treatment</th>
<th>Comparator</th>
<th>Clinical cure</th>
<th>Microbio. cure</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sano, 1979 (103), Japan</td>
<td>RCT</td>
<td>107, adults</td>
<td>UTI</td>
<td><em>Pseudomonas</em> spp. (mostly <em>P. aeruginosa</em>), <em>Proteus</em> spp. (mostly <em>P. mirabilis</em>)</td>
<td>2 x 2 g/day fosfomycin</td>
<td>2 x 2g/day sulbencillin</td>
<td>33/57 (56%) vs. 27/50 (54%)</td>
<td>23/57 (40%) vs. 20/50 (40%)</td>
<td>Good</td>
</tr>
<tr>
<td>Kobashi, 2002 (104), Japan</td>
<td>RCT</td>
<td>41, adults</td>
<td>Moderate^4 pneumonia</td>
<td><em>K. pneumoniae</em> (4), <em>S. pneumoniae</em> (4), MSSA (4), <em>P. aeruginosa</em> (3), MRSA (2), <em>K. oxytoca</em> (2), <em>H. influenzae</em>, <em>E. cloacae</em>, <em>S. marcescens</em>, <em>S. milleri</em>, <em>A. baumannii</em> (1 each)</td>
<td>2 x 2 g/day fosfomycin + 2 x 1 g/day sulbactam/cefpodoxime</td>
<td>2 x 1 g/day sulbactam/cefoxitin</td>
<td>17/18 (94%) vs. 15/17 (88%)</td>
<td>5/10 (50%) vs. 5/9 (56%)</td>
<td>Fair-good</td>
</tr>
<tr>
<td>Shimokata, 1988 (105), Japan</td>
<td>RCT</td>
<td>53, adults</td>
<td>RTI (mostly pneumonia)</td>
<td><em>H. influenzae</em> (4), <em>K. pneumoniae</em> (3), <em>S. aureus</em> (2), <em>S. galactica</em> (2), <em>S. viridans</em> (2), <em>Klebsiella</em> sp., <em>P. aeruginosa</em>, <em>S. epidermidis</em>, <em>H. parainfluenzae</em>, <em>E. faecium</em>, <em>E. aerogenes</em>, <em>S. pneumoniae</em> (1 each)</td>
<td>2 x 1-2 g/day fosfomycin + 2 x 1-2 g/day cefotaxime</td>
<td>cefotaxim</td>
<td>33/41 (80%) vs. 27/32 (84%)</td>
<td>10/11 (91%) vs. 4/4 (100%)</td>
<td>Poor-fair</td>
</tr>
<tr>
<td>Hiraoka, 1996 (63), Japan</td>
<td>RCT (Supplement)</td>
<td>161, age: NA</td>
<td>Bacteraemia/ Sepsis Pneumonia</td>
<td>Not reported</td>
<td>2 x 2 g/day fosfomycin + 2 x 1-2 g/day sulbactam/cefpodoxime</td>
<td>Sequence 1: Fos -&gt; Sul/Cef Sequence 2: Sul/Cef -&gt; Fos</td>
<td>45/76 (59%) vs. 30/69 (43%)</td>
<td>Not reported</td>
<td>Poor-fair</td>
</tr>
<tr>
<td>Sirijatuphat, 2014 (80), Thailand</td>
<td>RCT</td>
<td>104, adults</td>
<td><em>A. baumannii</em> infections (78% pneumonia)</td>
<td>Carbapenem resistant <em>A. baumannii</em></td>
<td>2 x 4 g/day fosfomycin + 5 mg/kg/day colistin (base activity)</td>
<td>5 mg/kg/day colistin (base activity)</td>
<td>30/47 (64%) vs. 27/47 (57%)</td>
<td>47/47 (100%) vs. 38/47 (81%); p = 0.01</td>
<td>Fair-good</td>
</tr>
<tr>
<td>Author, yr, country</td>
<td>Design</td>
<td>Patients, n</td>
<td>Infection</td>
<td>Isolated pathogens</td>
<td>Fosfomycin treatment</td>
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<tr>
<td>Ode, 1988 (93), Sweden</td>
<td>RCT</td>
<td>38, adults</td>
<td>Pyelonephritis</td>
<td><em>E. coli</em> (30), <em>Klebsiella</em> spp. (2), <em>P. vulgaris</em>, <em>P. aeruginosa</em>, <em>S. aureus</em>, <em>Enterococcus</em> sp. (1 each)</td>
<td>2 x 8 g/day fosfomycin</td>
<td>3 x 2 g ampicillin</td>
<td>7/16 (44%) vs. 6/22 (27%)</td>
<td>7/16 (44%) vs. 6/22 (27%)</td>
<td>Fair</td>
</tr>
<tr>
<td>Nissen, 1986 (106), Denmark</td>
<td>RCT</td>
<td>32, adults</td>
<td>Severe acute pneumonia</td>
<td>Coagulase neg. staphylococi (9), <em>Streptococcus pneumoniae</em> (6), <em>Streptococcus</em> spp. (4), <em>M. catarrhalis</em> (4), <em>E. coli</em> (7), <em>K. pneumoniae</em> (4), <em>H. influenzae</em> (2), <em>E. cloacae</em> (1), <em>P. aeruginosa</em> (3)</td>
<td>3 x 4 g/day fosfomycin + 3 x 80 mg gentamicin</td>
<td>4 x 1 g/day ampicillin + 3 x 80 mg gentamicin</td>
<td>10/17 (59%) vs. 7/15 (47%)</td>
<td>87.5% vs. 90% (no absolute numbers)</td>
<td>Fair</td>
</tr>
<tr>
<td>Zhang, 2003 (107), China</td>
<td>RCT</td>
<td>118, adults</td>
<td>lower RTI</td>
<td><em>S. pneumonia</em> (18), <em>K. pneumoniae</em> (17), <em>E. coli</em> (16), <em>S. epidermidis</em> (9), <em>H. verdigris</em> (9), <em>S. haemolyticus</em> (8), <em>P. aeruginosa</em> (7), <em>S. aureus</em> (3), <em>Acinetobacter</em> spp. (3)</td>
<td>8 g/day fosfomycin</td>
<td>4 g/day ceftriaxone</td>
<td>49/59 (83%) vs. 45/59 (76%)</td>
<td>75/90 (83%) vs. 68/85 (80%)</td>
<td>Fair</td>
</tr>
<tr>
<td>Otsuka, 1994 (108), Japan</td>
<td>Non-randomised controlled study</td>
<td>47, adults (15 cancer patients)</td>
<td>Primarily RTI (50% pneumonia)</td>
<td>MRSA (23), MRSA + secondary pathogen (39). Secondary pathogens: <em>P. aeruginosa</em> (14), <em>K. pneumoniae</em> (5), <em>Enterococcus</em> spp. (5) and others</td>
<td>2 x 2-4 g/day fosfomycin + 2 x 2 g/day cefmetazole</td>
<td>2 x 2-4 g/day fosfomycin + 2 x 2 g/day flomocef</td>
<td>16/22 (73%) vs. 14/22 (64%)</td>
<td>11/22 (50%) vs. 11/25 (44%)</td>
<td>Poor-fair</td>
</tr>
<tr>
<td>Albano, 1978 (109), Italy</td>
<td>Case-control study</td>
<td>64, pregnant women</td>
<td>Obstetric infections</td>
<td>Not reported</td>
<td>fosfomycin (dose not reported)</td>
<td>cefapirin (dose not reported)</td>
<td>35/38 (92%) vs. 22/26 (85%)</td>
<td>Not reported</td>
<td>Poor</td>
</tr>
<tr>
<td>Baron, 1987 (110), France</td>
<td>Case-control study</td>
<td>35, adults and children</td>
<td>primarily sepsis</td>
<td>MSSA</td>
<td>237 mg/kg/day fosfomycin + 145 mg/kg/day Penicillin M</td>
<td>3.6 mg/kg/day gentamycin + 113 mg/kg/day Penicillin M</td>
<td>16/17 (94%) vs. 14/18 (78%)</td>
<td>same as clinical</td>
<td>Poor-fair</td>
</tr>
<tr>
<td>Author, yr, country</td>
<td>Design</td>
<td>Patients, n</td>
<td>Infection</td>
<td>Isolated pathogens</td>
<td>Fosfomycin treatment</td>
<td>Comparator</td>
<td>Clinical cure</td>
<td>Microbio. cure</td>
<td>Quality</td>
</tr>
<tr>
<td>---------------------</td>
<td>--------</td>
<td>-------------</td>
<td>-----------</td>
<td>--------------------</td>
<td>---------------------</td>
<td>-----------</td>
<td>--------------</td>
<td>--------------</td>
<td>---------</td>
</tr>
<tr>
<td>Apisarnthananarak, 2012 (76), Thailand</td>
<td>Case-control study</td>
<td>49, adults</td>
<td>HAP, VAP</td>
<td>Carbapenem resistant <em>P. aeruginosa</em></td>
<td>Fosfomycin + Doripenem (dose not reported)</td>
<td>Fosfomycin + Colistin (dose not reported)</td>
<td>15/25 (60%) vs. 14/25 (56%)</td>
<td>18/25 (72%) vs. 15/24 (63%)</td>
<td>Poor</td>
</tr>
<tr>
<td>Matsumoto, 1993 (74), Japan</td>
<td>Non-randomised controlled study</td>
<td>19, adults</td>
<td>UTI, wound infections</td>
<td>MRSA</td>
<td>Fosfomycin + Cefuzonam (dose not reported)</td>
<td>Minocycline + Cefuzonam (dose not reported)</td>
<td>5/5 (100%) vs. 4/7 (57%)</td>
<td>same as clinical</td>
<td>Poor</td>
</tr>
<tr>
<td>Guerrero, 1986 (84), Spain</td>
<td>Case-control study</td>
<td>40, adults and children</td>
<td>Osteomyelitis</td>
<td><em>S. aureus</em> (33), <em>S. epidermidis</em> (4), <em>E. coli</em> (2), <em>E. faecalis</em> (2), <em>S. marcescens</em> (2), <em>M. tuberculosis</em> (2), <em>P. mirabilis</em>, <em>C. diversus</em>, <em>P. fluorescens</em>, <em>K. oxitoca</em>, <em>C. freundii</em>, <em>P. aeruginosa</em> (1 each)</td>
<td>150-200 mg/kg/day fosfomycin¹</td>
<td>150-200 mg/kg/day fosfomycin + various other antibiotics²</td>
<td>16/20 (80%) vs. 16/20 (80%)</td>
<td>19/20 (95%) vs. 18/20 (90%)</td>
<td>Poor</td>
</tr>
</tbody>
</table>

1. Fosfomycin dosage.
2. Other antibiotics included: *C. freundii*, *K. oxitoca*, *P. aeruginosa*, *S. marcescens*, *S. epidermidis*, *E. coli*, *E. faecalis*. |
<table>
<thead>
<tr>
<th>Author, yr, country</th>
<th>Design</th>
<th>Patients, n</th>
<th>Infection</th>
<th>Isolated pathogens</th>
<th>Fosfomycin treatment</th>
<th>Comparator</th>
<th>Clinical cure</th>
<th>Microbio. cure</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corti, 2003 (23), Switzerland</td>
<td>Case-control study</td>
<td>70, children</td>
<td>Osteomyelitis</td>
<td><em>S. aureus</em> (12), Coagulase neg. Staphylococci (6), <em>S. pyogenes</em> (2), <em>S. pneumonia</em> (1)</td>
<td>200 mg/kg/day fosfomycin (mono)</td>
<td>Comparator 1*: 200 mg/kg/day fosfomycin + various combination partners Comparator 2: Various antibiotics</td>
<td>Only C reactive protein value given over time as measure of response. Comparable in all groups. Duration of treatment shorter in fosfomycin monotherapy (p &lt; 0.05)</td>
<td>Not reported</td>
<td>poor</td>
</tr>
</tbody>
</table>

1Resistance development of 1 strain was noted during treatment (fosfomycin or comparator, respectively). 2Resistance development of 4 strains were noted during fosfomycin combination therapy. 3Resistance development of 2 strains were noted during fosfomycin combination therapy. 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*. 4Severity of diseases was not systematically reported by the authors. Indications are presented as per definitions of the respective authors.
Table 2. List of adverse events reported with intravenous fosfomycin use, categorized by their MedDRA preferred and high level terms. Relative number of occurrence is derived from the total number of studies for which adverse events have been reported (total patient number: 2672).

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>No. occurrence</th>
<th>Relative occurrence [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>140</td>
<td>5.24</td>
</tr>
<tr>
<td>Gastrointestinal disorders (unspecified)</td>
<td>69</td>
<td>2.56</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>16</td>
<td>0.60</td>
</tr>
<tr>
<td>Nausea</td>
<td>13</td>
<td>0.49</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>31</td>
<td>1.16</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9</td>
<td>0.34</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1</td>
<td>0.04</td>
</tr>
<tr>
<td>Retching</td>
<td>1</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypokalaemia</td>
<td>78</td>
<td>2.92</td>
</tr>
<tr>
<td>Hypernatraemia</td>
<td>18</td>
<td>0.68</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>1</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>19</td>
<td>0.71</td>
</tr>
<tr>
<td>Rash morbilliform</td>
<td>2</td>
<td>0.07</td>
</tr>
<tr>
<td>Urticaria</td>
<td>1</td>
<td>0.04</td>
</tr>
<tr>
<td>Erythema multiforme</td>
<td>1</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Injury, poisoning and procedural complications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Thrombo)phlebitis</td>
<td>16</td>
<td>0.60</td>
</tr>
<tr>
<td>Venous intolerance</td>
<td>11</td>
<td>0.41</td>
</tr>
<tr>
<td><strong>Altered laboratory parameters</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic enzyme increased (unspecified)</td>
<td>59</td>
<td>2.21</td>
</tr>
<tr>
<td>Transaminases increased (unspecified)</td>
<td>20</td>
<td>0.75</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>5</td>
<td>0.19</td>
</tr>
<tr>
<td>Laboratory test abnormal (unspecified)</td>
<td>5</td>
<td>0.19</td>
</tr>
<tr>
<td>Blood alkaline phosphatase increased</td>
<td>5</td>
<td>0.19</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>3</td>
<td>0.11</td>
</tr>
<tr>
<td>Blood bilirubin increased</td>
<td>2</td>
<td>0.07</td>
</tr>
<tr>
<td>Blood urea increased</td>
<td>2</td>
<td>0.07</td>
</tr>
<tr>
<td>Blood creatinine increased</td>
<td>1</td>
<td>0.04</td>
</tr>
<tr>
<td>Respiratory rate increased</td>
<td>1</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia*</td>
<td>6</td>
<td>0.22</td>
</tr>
<tr>
<td>Anaemia</td>
<td>5</td>
<td>0.19</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>4</td>
<td>0.15</td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>3</td>
<td>0.11</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>1</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oedema</td>
<td>6</td>
<td>0.22</td>
</tr>
<tr>
<td>Adverse event</td>
<td>No. occurrence</td>
<td>Relative occurrence [%]</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>----------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>Asthenia</td>
<td>4</td>
<td>0,15</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>3</td>
<td>0,11</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>3</td>
<td>0,11</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>1</td>
<td>0,04</td>
</tr>
<tr>
<td>Nicolau syndrome*¹</td>
<td>1</td>
<td>0,04</td>
</tr>
<tr>
<td>Flush</td>
<td>1</td>
<td>0,04</td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td><strong>6</strong></td>
<td><strong>0,22</strong></td>
</tr>
<tr>
<td>Systemic candidasis*</td>
<td>2</td>
<td>0,07</td>
</tr>
<tr>
<td>Fungal infection</td>
<td>2</td>
<td>0,07</td>
</tr>
<tr>
<td>Herpes simplex infection</td>
<td>2</td>
<td>0,07</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td><strong>16</strong></td>
<td><strong>0,60</strong></td>
</tr>
<tr>
<td>Headache</td>
<td>14</td>
<td>0,52</td>
</tr>
<tr>
<td>Vertigo</td>
<td>1</td>
<td>0,04</td>
</tr>
<tr>
<td>Hyperosmolar coma* + hyperglycaemia</td>
<td>1</td>
<td>0,04</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td><strong>5</strong></td>
<td><strong>0,19</strong></td>
</tr>
<tr>
<td>Hypertension</td>
<td>2</td>
<td>0,07</td>
</tr>
<tr>
<td>Vascular pain</td>
<td>2</td>
<td>0,07</td>
</tr>
<tr>
<td>Shock*</td>
<td>1</td>
<td>0,04</td>
</tr>
<tr>
<td><strong>Cardiac disorders</strong></td>
<td><strong>9</strong></td>
<td><strong>0,34</strong></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>3</td>
<td>0,11</td>
</tr>
<tr>
<td>Cardiac failure*²</td>
<td>2</td>
<td>0,07</td>
</tr>
<tr>
<td>Pain in the heart*</td>
<td>2</td>
<td>0,07</td>
</tr>
<tr>
<td>Cardiac disorders (unspecified)</td>
<td>2</td>
<td>0,07</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td><strong>16</strong></td>
<td><strong>0,60</strong></td>
</tr>
<tr>
<td>Worsening of pulmonary oedema* in patients with heart insufficiency and endocarditis</td>
<td>2</td>
<td>0,07</td>
</tr>
<tr>
<td>Cough</td>
<td>1</td>
<td>0,04</td>
</tr>
<tr>
<td>Abnormal Fishberg test</td>
<td>1</td>
<td>0,04</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>1</td>
<td>0,04</td>
</tr>
<tr>
<td>Flushing</td>
<td>1</td>
<td>0,04</td>
</tr>
<tr>
<td>Unspecified side effects</td>
<td>10</td>
<td>0,37</td>
</tr>
</tbody>
</table>

* 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.

1) Nicolau syndrome occurred in a patient which was treated with fosfomycin intramuscularly.
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.
Records identified through database searching in PubMed (n = 287)
Records identified through database searching in the Cochrane Library (n = 135)
Additional records identified through hand search of articles (n = 137)

Total records PubMed + Cochrane + additional records (n = 559)

Duplicates (n = 86)

Title and abstract screened (n = 473)

Records did not match inclusion criteria (n = 318)

Full-text articles assessed for eligibility (n = 155)

Records did not match inclusion criteria (n = 27)

Studies included in systematic review (Total: n = 128, comparative: n = 17, non-comparative: n = 111)
Fig. 2

(a) Sepsis, bacteraemia, 1492, 27%
- Respiratory tract infections, 950, 17%
- CNS infections, 619, 8%
- Bladder, 747, 13%
- Other, 573, 10%
- Cardiac infections, 42; 1%
- Non-site specific injuries and procedural complications, 88; 2%
- Female reproductive tract infections, 110; 2%
- SSTI, 168; 3%
- Abdominal and GI infections, 267; 5%

(b) Staphylococcus spp., 1408, 41%
- Escherichia coli, 564, 16%
- Pseudomonas spp., 465, 13%
- Serratia spp., 133, 4%
- Other, 178; 5%
- Enterococcus spp., 114; 3%
- Klebsiella spp., 218; 6%
- Proteus spp., 355; 4%
### Monotherapy

<table>
<thead>
<tr>
<th>Author(s) and Year</th>
<th>Fosfomycin Effec.</th>
<th>Comparator Effec.</th>
<th>Fosfomycin Total</th>
<th>Comparator Total</th>
<th>OR [95% CI]</th>
<th>OR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhang 2003</td>
<td>49</td>
<td>59</td>
<td>45</td>
<td>59</td>
<td>1.52</td>
<td>[0.62, 3.78]</td>
</tr>
<tr>
<td>Sano 1979</td>
<td>33</td>
<td>57</td>
<td>27</td>
<td>50</td>
<td>1.17</td>
<td>[0.54, 2.52]</td>
</tr>
<tr>
<td>Ode 1988</td>
<td>7</td>
<td>16</td>
<td>6</td>
<td>22</td>
<td>2.07</td>
<td>[0.53, 8.10]</td>
</tr>
<tr>
<td>Albano 1978</td>
<td>38</td>
<td>38</td>
<td>26</td>
<td>26</td>
<td>Not estimable</td>
<td></td>
</tr>
</tbody>
</table>

**RE Model for Subgroup**

1.41 [0.83, 2.39]

### Combination Therapy

<table>
<thead>
<tr>
<th>Author(s) and Year</th>
<th>Fosfomycin Effec.</th>
<th>Comparator Effec.</th>
<th>Fosfomycin Total</th>
<th>Comparator Total</th>
<th>OR [95% CI]</th>
<th>OR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sirijatuphat 2014</td>
<td>30</td>
<td>47</td>
<td>27</td>
<td>47</td>
<td>1.31</td>
<td>[0.57, 3.00]</td>
</tr>
<tr>
<td>Shimokata 1988</td>
<td>33</td>
<td>41</td>
<td>27</td>
<td>32</td>
<td>0.76</td>
<td>[0.22, 2.61]</td>
</tr>
<tr>
<td>Nilsson 1986</td>
<td>16</td>
<td>14</td>
<td>12</td>
<td>15</td>
<td>4.00</td>
<td>[0.37, 43.38]</td>
</tr>
<tr>
<td>Matsumoto 1993</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>7</td>
<td>8.56</td>
<td>[0.34, 212.94]</td>
</tr>
<tr>
<td>Kobashi 2002</td>
<td>17</td>
<td>18</td>
<td>15</td>
<td>17</td>
<td>2.27</td>
<td>[0.19, 27.58]</td>
</tr>
<tr>
<td>Baron 1987</td>
<td>16</td>
<td>17</td>
<td>14</td>
<td>18</td>
<td>4.57</td>
<td>[0.46, 45.66]</td>
</tr>
</tbody>
</table>

**RE Model for Subgroup**

1.48 [0.81, 2.71]

**RE Model for All Studies**

1.44 [0.96, 2.15]

### Heterogeneity

- $\text{Tau}^2 = 0$;
- $Q(\text{df} = 9) = 4.62$; $I^2 = 0\%$; $p = 0.87$
- Test for overall effect: $Z = 1.78$; $p = 0.07$
- RE: Random effects

**Fig. 3**