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Review

Susceptibility of contemporary isolates to fosfomycin: a systematic review of the literature

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ABSTRACT

The aim of this review was to evaluate the susceptibility of contemporary Gram-positive and Gram-negative bacteria to fosfomycin. PubMed and Scopus databases were systematically searched to identify studies published in print or electronically from January 2010 until June 2015. In total, 84 studies were selected. Susceptibility to fosfomycin of *Staphylococcus aureus* ranged between 33.2% and 100% (odds ratio = 91.7%, 95% confidence interval 88.7–94.9%), of *Enterococcus* spp. from 30% to 100% (*Enterococcus faecium* 92.6%, 85.2–100%; *Enterococcus faecalis* 96.8%, 92.5–100%), of extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* from 81% to 100% (95.1%, 94.3–95.9%), of ESBL-producing *Klebsiella pneumoniae* from 15% to 100% (83.8%, 78.7–89.4%) and of carbapenem-resistant (CR) *K. pneumoniae* from 39.2% to 100% (73.5%, 66.4–81.4%). *Staphylococcus aureus* (including meticillin-resistant strains) and *E. coli* (including ESBL-producing strains) were the most likely to be susceptible with low minimum inhibitory concentrations (MICs). Enterococci (particularly vancomycin-resistant *E. faecium*) and *K. pneumoniae* (especially CR strains) were less susceptible with higher MIC_{50} and MIC_{90} values. Two studies reported decreasing susceptibility of ESBL-producing *E. coli* to fosfomycin. In conclusion, guided by local susceptibility data, fosfomycin could be considered for the treatment of patients with infections due to problematic multidrug-resistant bacteria.

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1. Introduction

The development of multidrug resistance and extensive drug resistance in bacteria limits available treatment options for infections caused by these organisms [1]. As new antibiotics are either rare or expensive, older ones that retain activity against multidrug-resistant (MDR) bacteria have attracted the attention of researchers. Polymyxins have already become a standard of care in intensive care unit patients with extensively drug-resistant (XDR) infections [2,3]. Among older antibiotics, fosfomycin also appears to be a possible alternative because it has a broad spectrum of activity both against Gram-positive and Gram-negative bacteria and is widely distributed in tissues while retaining high serum concentrations [4,5].

Most of the available data regarding fosfomycin come from older studies and their relevance to contemporary practice is debated. Previous reviews concluded that fosfomycin was active against MDR bacteria, including meticillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae [6–8]. However, studies showed that fosfomycin resistance increases in areas with higher consumption [9]. In addition, new plasmid-mediated mechanisms of resistance have been identified [10].

In this systematic review, we sought to summarise the evidence from contemporary studies and evaluated the activity of fosfomycin against MDR and XDR bacteria.

2. Methods

PubMed and Scopus databases were searched to identify studies evaluating the in vitro activity of fosfomycin against bacteria grown

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from clinical specimens regardless of the method used for bacterial identification, susceptibility testing method and criteria for interpretation [i.e. European Committee on Antimicrobial Susceptibility Testing (EUCAST) or Clinical and Laboratory Standards Institute (CLSI)]. The search terms used were 'fosfomycin AND (resistan* OR susceptibil* OR sensitiv* OR activ*)'. Only studies published electronically or in print from January 2010 to June 2015 were selected. Studies evaluating synergism or antagonism as well as clinical studies were excluded.

When possible, a meta-analysis was used to estimate the pooled proportion of susceptible isolates according to bacterial species, specific resistance profiles and regions of the globe. Statistical analyses were performed using the meta and metafor packages in R (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/). A random-effects model was used as significant heterogeneity was expected. Heterogeneity was studied using a χ^2 test, and the degree of heterogeneity with I^2. A P-value of <0.05 was defined to denote statistical significance.

3. Results

In total, 1472 articles were retrieved from PubMed and 4494 from Scopus, among which 496 and 1425 published from January 2010 until June 2015 were included from PubMed and Scopus, respectively. Finally, 84 articles were selected for inclusion in the review.

3.1. Gram-positive bacteria (Table 1)

3.1.1. Staphylococcus *spp.*

The susceptibility of *S. aureus* to fosfomycin ranged between 33.2% and 100% in the nine available studies (odds ratio = 91.7%, 95% confidence interval 88.7–94.9%; I^2 = 97.3%); in seven of the studies susceptibility was >90% [11–19]. Susceptibility was similarly high for meticillin-resistant and -susceptible strains in all but one study [19]. The MIC_{50} and MIC_{90} values [minimum inhibitory concentrations (MICs) that inhibit 50% and 90% of the isolates, respectively] were provided in two studies [13,19]. In one they were low (1 mg/L and 16 mg/L, respectively) [19] and in one they were high (64 mg/L and 128 mg/L, respectively) [13]. Susceptibility to vancomycin and tigecycline was high. Data regarding other antibiotics were not collected. The susceptibility of coagulase-negative staphylococci to fosfomycin varied between 77.5% and 100% in the five available studies [14,16,18,20,21]. The MIC_{50} and MIC_{90} values were not reported.

3.1.2. Enterococcus *spp.*

Nine studies provided data for *Enterococcus* spp. Fosfomycin was active against 30–100% of the tested strains [13,16,18,22–27]. Vancomycin resistance did not appear to be associated with lower susceptibility to fosfomycin. In a few studies, *Enterococcus faecium* (92.6%, 85.2–100%; I^2 = 81.5%) was slightly less susceptible to fosfomycin than *Enterococcus faecalis* (96.8%, 92.5–100%; I^2 = 60.2%) [13,24,27], but this was not observed in all available studies [22]. When reported, MIC_{50} and MIC_{90} values of VRE strains were >32 mg/L.

3.1.3. Other Gram-positive bacteria

Streptococcus pneumoniae was evaluated in two studies. Susceptibility was 61.9% and 100%; MIC_{50} and MIC_{90} values were not provided [21,28]. In the single study that provided data for *Streptococcus pyogenes* and *Streptococcus agalactiae*, susceptibility to fosfomycin was 40.6% and 56%, respectively [21]. Finally, two studies provided data for all Gram-positive isolates without differentiating between individual species. Both reported susceptibility of Gram-positive bacteria to fosfomycin to be ca. 73% [29,30].

3.2. Gram-negative bacteria

3.2.1. Extended-spectrum β-lactamase-producing strains

The majority of data regarding fosfomycin activity against ESBL-producing strains refer to *Escherichia coli* and to a lesser extent *Klebsiella pneumoniae* isolated from urine samples (Table 2) [16,18,25,31–66]. The reported susceptibility of *E. coli* strains ranged from 81% to 100% (95.1%, 94.3–95.9%; I^2 = 98.9%). The MIC_{50} and MIC_{90} values were usually low (below 2–4 mg/L), but a few studies, mainly from Asian countries, reported higher MIC_{90} values up to 128 mg/L [47,48,57,59,61]. Susceptibility in developed countries (96%, 95–97%; I^2 = 99.2%) was slightly higher than in developing countries (93.4%, 90.5–96.4%; I^2 = 95.2%). Use of EUCAST or CLSI criteria did not appear to affect the reported susceptibility rates, since most of the *E. coli* isolates had a relatively low MIC (≤4 mg/L). A significant decrease in susceptibility to fosfomycin was observed for *E. coli* strains in two Spanish studies [62,64]. The decrease was rapid in one of them (from 100% to 85.6%) but was slower in the other (from 97.8% to 95.5%). Data regarding antibiotic consumption were not available.

For *K. pneumoniae* strains the susceptibility varied between 15% and 100% (83.8%, 78.7–89.4%; I^2 = 92.8%). The MIC_{50} and MIC_{90} values ranged between <1 mg/L and <48 mg/L, and 32 and >1024 mg/L, respectively, but most of the studies reported high MIC_{50} and MIC_{90} values. Susceptibility in developed countries (87.4%, 77.9–98.2%; I^2 = 85.8%) was slightly higher than in developing countries (82.4%, 76.1–89.3%; I^2 = 94.3%). The lowest susceptibility rate (15%) was reported in a study that used the EUCAST criteria for evaluating *K. pneumoniae* strains [65]. However, not all studies using EUCAST criteria reported low susceptibility [48,59]. In one study that used both CLSI and EUCAST criteria, susceptibility to fosfomycin was similar (83.8% and 81.1%, respectively) [59].

Susceptibility to fosfomycin was higher among CTX-M-producing *E. coli* strains than CTX-M-producing *K. pneumoniae* strains [65,66]. Both *E. coli* and *K. pneumoniae* strains were more susceptible to fosfomycin than gentamicin; variable outcomes have been reported with amikacin. The few available data suggest that fosfomycin was similarly active to tigecycline and colistin [32,36,44,46,47,51,59,60,62,65]. ESBL-producing strains were usually, but not uniformly, highly susceptible to carbapenems.

Three studies reported data regarding *Proteus* spp. [18,42,50]; susceptibility to fosfomycin ranged between 50% and 72%. All *Citrobacter* spp. were susceptible to fosfomycin, whilst susceptibility of *Enterobacter* spp. was lower (75–93.7%) [42,50].

3.2.2. Carbapenem-resistant (CR) bacteria

Thirteen studies reported on the activity of fosfomycin against CR Gram-negative bacteria [24,48,67–77] (Table 3). Twelve of them studied *Klebsiella* spp., mainly KPC-producing *K. pneumoniae* [24,48,68–77]. The reported susceptibility ranged between 39.2% and 100% (73.5%, 66.4–81.4%; I^2 = 96.8%). The lowest susceptibility was seen in KPC-producing isolates that also carried *fosA*, a plasmid-mediated gene producing a metalloenzyme that inactivates fosfomycin [48]. Low susceptibility was also seen in KPC-producing isolates that carried the *rmtB* gene (which produces 16S RNA methylases that confer resistance to aminoglycosides) [69]. Interpretation with EUCAST criteria did not appear to affect susceptibility reports compared with CLSI criteria (EUCAST defines susceptible isolates as those with an MIC ≤ 32 mg/L compared with the CLSI at MIC ≤ 64 mg/L), except for one study that compared the two criteria [77]. The same study reported differences (more than two dilutions) between agar dilution and Etest. There did not appear to be any difference in susceptibility between

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