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Synergy of fosfomycin with other antibiotics for Gram-positive and Gram-negative bacteria

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Abstract

Background The alarming increase in drug resistance and decreased production of new antibiotics necessitate the evaluation of combinations of existing antibiotics. Fosfomycin shows no cross-resistance to other antibiotic classes. Thus, its combination with other antibiotics may potentially show synergy against resistant bacteria.

Objective To evaluate the available published evidence regarding the in vitro synergistic activity of fosfomycin with other antibiotic agents against Gram-positive and Gram-negative bacteria.

Methods PubMed and the Cochrane Library were searched. **Results** Forty-one studies, including 34 (82.9%) conducted/published before 2000, were eligible for inclusion. The relatively limited number of isolates examined and the considerable heterogeneity of the retrieved studies regarding the definitions of synergy and the methodologies used hamper conclusive remarks for specific combinations of fosfomycin

with other antibiotics. Yet, in the 27 studies providing data for Gram-positive strains (16 for *Staphylococcus aureus*, 3 for coagulase-negative staphylococci, 5 for *Streptococcus pneumoniae*, and 3 for *Enterococcus* spp.), fosfomycin showed synergy against methicillin-resistant *Staphylococcus aureus* when combined with cefamandole, cephazolin, ceftriaxone, ciprofloxacin, imipenem, and rifampicin. Data regarding Gram-negative strains reported from 15 studies (12 exclusively for *P. aeruginosa*, 2 exclusively for Enterobacteriaceae, 1 for both, and 1 for *Acinetobacter baumannii*) suggested that fosfomycin showed an estimable synergistic effect with gentamicin, amikacin, ceftazidime, cefepime, ciprofloxacin, levofloxacin, and aztreonam against *P. aeruginosa*.

Conclusions The synergistic combination of fosfomycin with other antibiotics may be a useful alternative treatment option for Gram-negative and Gram-positive infections. Additional studies using more stringent definitions of synergy, and studies reporting on the clinical efficacy of fosfomycin combinations in the current era of high antimicrobial resistance are needed.

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Keywords Drug-resistance · Synergistic combinations · Antagonism · MRSA · ESBLs

Introduction

The alarmingly increasing drug resistance rates observed in our era limit our armamentarium of antibiotics and necessitate the development and evaluation of alternative ways to cope with this issue. Specifically, the renewal of physicians' interest in older and neglected antibiotic agents [1, 2], as well as the use of combinations of antibiotic agents for the treatment of patients with infections may be useful “weapons” in the “battle” against antimicrobial resistance.

Fosfomycin is an old antibiotic agent that has been used for the treatment of uncomplicated urinary tract infections in many clinical settings [3, 4]. Additionally, data reported from recent studies encourage the use of fosfomycin for the treatment of infections beyond the urinary tract [5, 6] as well as for infections due to specific categories of resistant bacteria [7, 8]. Consequently, a potential synergistic activity of fosfomycin with other antibiotic agents may prove to be an important issue with considerable clinical implications.

In this regard, we aimed to collect and evaluate the available evidence regarding the *in vitro* synergistic activity of fosfomycin in combination with other antibiotic agents against Gram-negative and Gram-positive bacteria.

Methods

Literature search

We searched the PubMed and the Cochrane Library databases. The search strategy applied to these databases was “(fosfomycin OR phosphomycin OR fosfonomycin) AND (synergy OR synergism OR combination OR antagonism).” Bibliographies of relevant articles were also hand-searched.

Study selection criteria

A study was considered as eligible for inclusion if it provided data regarding the *in vitro* use of fosfomycin in combination with other antibiotic agents against Gram-positive and/or Gram-negative microbial strains. Studies written in languages other than English, Spanish, French, German, Italian, or Dutch were excluded. Abstracts from scientific conferences were also excluded.

Data extraction

We extracted data regarding the laboratory methods used, the fosfomycin break point, the susceptibility of the pathogens to fosfomycin, the pathogens isolated, the site of isolation, and the type of antibiotics used in the combined therapy. Data regarding the number of bacterial strains for which synergism between fosfomycin and other selected antibiotic agents was observed were also extracted.

Results

Selected studies

Our searches performed in PubMed and the Cochrane Library generated a total of 411 and 36 articles, respectively. Among

these, 41 studies were considered eligible for inclusion in our review [9–49].

Characteristics of the included studies

Twenty-seven of the 41 included studies provided data regarding the number of Gram-positive strains for which a synergistic effect of fosfomycin with other selected antibiotic agents was exhibited [10, 13, 15, 19, 21, 23–26, 28–33, 35–44, 46, 47]. Fifteen of the 41 included studies provided data regarding the number of Gram-negative strains for which a synergistic effect of fosfomycin with other selected antibiotic agents was exhibited [9, 11, 12, 14, 16–18, 20, 22, 27, 34, 45, 47–49]. One of the 41 included studies provided data regarding the number of Gram-positive as well as Gram-negative strains for which a synergistic effect of fosfomycin with other selected antibiotic agents was exhibited [47].

The definition of *synergy* used by the majority of the included studies (25 of the 41 included) was the fractional inhibitory concentration index (FICI), represented by the formula $FICI = (\text{MIC of fosfomycin in combination} / \text{MIC of fosfomycin alone}) + (\text{MIC of the antibiotic in combination} / \text{MIC of the antibiotic alone})$, where MIC is the minimal inhibitory concentration. The efficacy time index (ETI) technique was also used in two of the included studies for the assessment of the synergistic effect of fosfomycin with the evaluated antibiotics [13, 14]. Detailed data regarding the laboratory methods used, the fosfomycin break points, the definition of synergy used, the antibiotics evaluated, as well as the pathogens evaluated along with the site of isolation are presented, when available, in Table 1.

Synergy of fosfomycin with other antibiotics

Gram-positive strains

Thirteen studies provided data regarding the *in vitro* synergistic effect of fosfomycin with other antibiotics against MRSA strains [13, 19, 26, 29–31, 36, 41–44, 46]. The study examining the largest number of MRSA strains reported a good synergistic effect of fosfomycin with cefamandole and with methicillin (65.5 and 31% of the 148 tested strains, respectively) [42]. However, the findings of this study were not encouraging regarding the potential synergistic effect of fosfomycin with gentamicin, trimethoprim, and vancomycin [42]. Two other studies providing data for a considerable number of MRSA strains reported a synergistic effect of 100% for the combination of fosfomycin with cefamandole [44], and a synergistic effect of 94.2% for the combination of fosfomycin with ceftazidime [31]. Encouraging relevant data were also reported from

Table 1 Main characteristics of the studies included in the review

First author, year [ref]	Laboratory method	Fosfomycin break point	Definition of synergy	Antibiotics evaluated	Pathogens evaluated/site of isolation
Yamada et al., 2007 [9]	Broth microdilution	CLSI criteria	FICI \leq 0.5	Ciprofloxacin	Ciprofloxacin-resistant <i>P. aeruginosa</i> /NR
Sahuquillo Arce et al., 2006 [10]	Checkerboard method	Lowest concentration that prevented growth after 24 h, NR	FICI \leq 0.5	Linezolid	MSSA/NR
Mikuniya et al., 2005 [11]	Checkerboard method	NR	FICI \leq 0.5	Ulifloxacin Levofloxacin	<i>P. aeruginosa</i> /NR
Pruekprasert et al., 2005 [12]	Checkerboard titration method	CLSI criteria	FICI \leq 0.5	Gentamicin Ceftazidime Imipenem	<i>P. aeruginosa</i> /NR
Nakazawa et al., 2003 [13]	Broth microdilution method designed by the Japanese Society of Chemotherapy	NR	ETI assay 1–8 index=synergy	Imipenem Cefmetazole Sulbactam/cefoperazone Panipenem Ampicillin Cefotiam Flomoxef sodium Arbekacin Vancomycin Minocycline Ofloxacin	MRSA/wounds of burn patients
Okazaki et al., 2002 [14]	Efficiency time index assay	\leq 16	ETI \geq 1 to <8 good synergism, \geq 8 excellent synergism	Cefepime Ceftazidime Aztreonam Imipenem Meropenem Gentamicin Piperacillin Levofloxacin	<i>P. aeruginosa</i> /NR
Grif et al., 2001 [15]	Checkerboard method and killing curve method	\leq 16	NR	Rifampicin Linezolid Quinupristin/dalfopristin Moxifloxacin Vancomycin Cefazolin Meropenem	<i>S. epidermidis</i> , <i>S. aureus</i> /catheter tip
Hayami et al., 1999 [16]	Checkerboard method and killing curve method, agar dilution	NR	FICI \leq 0.5	Meropenem Amikacin Ceftazidime Ciprofloxacin	<i>P. aeruginosa</i> /UTI
Traub et al., 1998 [17]	Time kill	CLSI criteria	NR	Amikacin	MDR <i>P. aeruginosa</i> /trachea
Dubrous et al., 1997 [18]	Agar dilution	\leq 16	NR	Ceftazidime	<i>P. aeruginosa</i> /NR

Table 1 (continued)

First author, year [ref]	Laboratory method	Fosfomycin break point	Definition of synergy	Antibiotics evaluated	Pathogens evaluated/site of isolation
Ferrara et al., 1997 [19]	Broth microdilution, time killing experiments	$R \geq 32$	A decrease in cfu ≥ 2 log of the antibiotic combination at 24 h when compared with the most effective single drug	Sparfloxacin Oxacillin	MRSA, MRSE/NR
Tessier et al., 1997 [20]	Checkerboard method	≤ 16	FICI ≤ 0.5	Ceftazidime Imipenem Amikacin Ciprofloxacin	<i>P. aeruginosa</i> /NR
Totsuka et al., 1997 [21]	Checkerboard and broth microdilution	Japanese guidelines	FICI ≤ 0.5	Cefepime Cefminoxe Benzylpenicillin Imipenem Cefazolin Cefotiam Cefotaxime	Penicillin resistant <i>S. pneumoniae</i> /NR
Martinez-Martinez et al., 1996 [22]	Checkerboard microdilution method	CLSI criteria	FICI ≤ 0.5	Imipenem Ceftazidime Ciprofloxacin Amikacin Tobramycin	<i>Acinetobacter baumannii</i> /NR
Kikuchi et al., 1995 [23]	Checkerboard method, broth microdilution	NR	FICI < 1.0 FICI ≤ 0.5	Benzylpenicillin	Penicillin-resistant <i>S. pneumoniae</i> /NR
Pestel et al., 1995 [24]	Checkerboard method	CASFM	FICI ≤ 0.5	Cefotaxime	Enterococci/blood
Doit et al., 1994 [25]	Agar dilution	NR	Increase in killing of at least 2 log ₁₀ CFU/ml relative to the killing of the most active agent of the combination used alone	Ceftriaxone Imipenem Vancomycin	<i>S. pneumoniae</i> , penicillin resistant/CSF
Drungeon et al., 1994 [26]	Checkerboard method	CLSI criteria	Area under the killing curve, decrease of at least 16% after 6 h in the area under the curve of survivors	Fusidic acid	MRSA, MSSA/NR
Watine et al., 1994 [27]	Broth microdilution	NR	Time kill and combination	Ceftazidime Aztreonam Imipenem Amikacin	<i>P. aeruginosa</i> /NR
Barakett et al., 1992 [28]	Agar dilution and killing curves	≤ 16	Increase in killing of at least 2 log ₁₀ CFU/ml relative to the killing of the most active agent of the combination used alone	Cefotaxime	<i>S. pneumoniae</i> /Pulmonary secretions, CSF
Hamilton-Miller et al., 1992 [29]	Agar dilution, checkerboard method, paired disk method	≤ 64	FICI ≤ 0.70	Rifampicin Ciprofloxacin	MRSA, coagulase(-) staphylococci, enterococci/NR
Matsuda et al., 1991 [30]	Checkerboard agar dilution method	NR	FICI ≤ 0.5	Cefmetazole	MRSA also imipenem resistant/NR
Chang et al., 1989 [31]	Checkerboard titration method	Lowest concentration where no growth was observed	FICI ≤ 0.5	Cefmetazole Cefazolin	MRSA/NR

Table 1 (continued)

First author, year [ref]	Laboratory method	Fosfomycin break point	Definition of synergy	Antibiotics evaluated	Pathogens evaluated/site of isolation
Gatermann et al., 1989 [32]	Agar dilution	≤16	FICI≤0.5	Vancomycin	<i>S. aureus</i> , <i>S. epidermidis</i> / abscesses, wound infections, endocarditis, foreign body infections, UTI
Rice et al., 1989 [33]	Agar dilution, time kill experiments	64	Time-kill techniques	Daptomycin	High-level gentamicin resistance, <i>Enterococcus faecalis</i> /NR
Figuerdo et al., 1988 [34]	Agar plate dilution checkerboard method	NR	FICI≤0.5	Ciprofloxacin Ofloxacin	<i>P. aeruginosa</i> /sputum
Courcol et al., 1987 [35]	Checkerboard method and killing curve method, broth microdilution for the MIC combinations	≤25	FICI≤0.5	Ceftriaxone	<i>S. aureus</i> (3 MRSA), <i>S. epidermitis</i> (3 MRSE); all strains beta lactamase producing/blood
David et al., 1987 [36]	Checkerboard method	NR	FIC≤0.5	Ceftriaxone	MRSA, MSSA/NR
May et al., 1987 [37]	Microbroth dilution	NR	FICI≤0.5	Ceftriaxone	<i>S. aureus</i> , <i>S. pneumoniae</i> , <i>Klebsiella</i> spp., <i>Peptococcus</i> /CSF
Ullmann et al., 1987 [38]	Checkerboard	NR	FICI≤0.5	Ciprofloxacin	<i>P. aeruginosa</i> , <i>S. aureus</i> /NR
Debbia et al., 1986 [39]	Checkerboard method and killing curve method	R ≥ 32	FICI≤0.5	Imipenem	<i>E. faecalis</i> , <i>E. faecium</i> , <i>S. aureus</i> (16 MRSA), <i>S. epidermidis</i> (7 MRSE), <i>Staphylococcus</i> spp./NR
Stahl et al., 1986 [40]	Microdilution	NR	FICI≤0.5	Ceftriaxone	<i>S. epidermidis</i> , <i>S. aureus</i> , <i>Neisseria meningitidis</i> , <i>S. pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>Serratia marcescens</i> , <i>Aeromonas hydrophila</i> /CSF
Utsui et al., 1986 [41]	Checkerboard	NR	FICI≤0.5	Cefmetazole Cefaloridine Cefotaxime	MRSA/NR
Alvarez et al., 1985 [42]	Agar dilution	≤16	MICs of both drugs decreased by at least 1/4	Vancomycin Gentamicin Cefamandole Methicillin Trimethoprim	MRSA/blood, sputum, wounds, urine, peritoneal fluid, and eyes
Portier et al., 1985 [43]	Checkerboard method	NR	FBC≤0.75	Cefotaxime Cefoperazone Cefamandole Cephalothin	MRSA also resistant to gentamicin/ CSF, bone and joint infection, thrombophlebitis
Fosse et al., 1984 [44]	Checkerboard method, broth microdilution	≤ 8	FICI≤0.5	Cefamandole Vancomycin Rifampicin	MR <i>Staphylococcus</i> spp., MRSA, MRSE/NR
Takahashi et al., 1984 [45]	Agar plate dilution checkerboard method	NR	FICI≤0.5	Piperacillin-tobramycin Piperacillin Cefoperazone Cefoperazone-tobramycin Cefsulodin Cefsulodin-tobramycin	<i>P. aeruginosa</i> /NR

Table 1 (continued)

First author, year [ref]	Laboratory method	Fosfomycin break point	Definition of synergy	Antibiotics evaluated	Pathogens evaluated/site of isolation
Tremeux et al., 1983 [46]	Checkerboard	NR	FICI \leq 0.5	Cefotaxime	MRSA/CSF
Olay et al., 1978 [47]	Agar plate checkerboard method	NR	4 times or greater reduction of the MIC of both antibiotics compared to the MIC of each antibiotic alone	Gentamicin Carbenicillin	<i>P. aeruginosa</i> , <i>S. aureus</i> , <i>Streptococcus</i> spp., <i>E. coli</i> , <i>Klebsiella</i> spp., <i>Proteus</i> spp., <i>Enterococcus cloacae</i> , <i>Salmonella</i> spp., <i>Serratia marcescens</i> /NR
Perea et al., 1978 [48]	Agar dilution method, checker board titration	NR	FICI \leq 0.75	Ampicillin Chloramphenicol	<i>Salmonella</i> spp., <i>Shigella</i> spp./NR
Baquero et al., 1977 [49]	Agar dilution, checkerboard method	\leq 32	FICI \leq 0.5	Gentamicin Carbenicillin	<i>Serratia marcescens</i> /NR

NR Not reported, R resistance, MIC minimum inhibitory concentration, FIC fractional inhibitory concentrations, FICI fractional inhibitory concentration index, MRSA methicillin-resistant *Staphylococcus aureus*, MSSA methicillin-susceptible *Staphylococcus aureus*, CSF cerebrospinal fluid, MRSE methicillin-resistant *Staphylococcus epidermidis*, CFU colony forming units, CLSI Clinical and Laboratory Standards Institute, UTI urinary tract infections, ETI efficacy time index, FBC fractional bactericidal concentration

several other studies, although the number of the evaluated MRSA was rather limited. Specific data are shown in Table 2.

Nine studies provided data regarding the in vitro synergistic effect of fosfomycin with other antibiotics against *Staphylococcus aureus* and/or other coagulase-negative *Staphylococcus* strains [29, 32, 35–40, 47]; specific data are shown in Table 2. Notably, a synergistic effect of fosfomycin with ciprofloxacin was reported for 51.3% of the 37 *S. aureus* tested strains [38]. The findings regarding gentamicin were discouraging (0 of the 29 *S. aureus* tested strains) [47]. Relevant data regarding *Streptococcus* spp. were reported from five studies [21, 23, 25, 28, 37]. A similar synergistic effect of fosfomycin was reported with penicillin [21], cefminox [21], cefotaxime [28], and cefotiam [21]. Specific data are shown in Table 2.

Three studies provided data regarding the in vitro synergistic effect of fosfomycin with other antibiotics against *Enterococcus* spp. [24, 33, 39]. A synergistic effect of 90% was reported for the combination of fosfomycin with cefotaxime from a study analyzing a total of 50 strains [24]. Data regarding the combination of fosfomycin with daptomycin [33] or imipenem [39] were also encouraging.

Gram-negative strains

Thirteen studies provided data regarding the in vitro synergistic effect of fosfomycin with other antibiotics against *Pseudomonas aeruginosa* strains [9, 11, 12, 14, 16–18, 20, 27, 34, 38, 45, 47]. In one of the above-mentioned studies providing data for 30 *P. aeruginosa* strains [14], fosfomycin exhibited a synergistic effect in \geq 70% of the tested strains when it was used in combination

with aztreonam, cefepime, ceftazidime, gentamicin, imipenem, and levofloxacin. Two other studies evaluated the potential synergistic effect of fosfomycin with ciprofloxacin, reporting data for 74 and 37 *P. aeruginosa* strains, respectively; the observed synergistic effect was 27% [9] and 78.4% [38], respectively. Three other studies evaluated the potential synergistic effect of fosfomycin with amikacin against *P. aeruginosa* [17, 20, 27]. The observed synergistic effect ranged from 18.8 to 100%. Yet, the number of the analyzed strains in each of these four studies was limited (maximum 26 strains).

A single study provided data regarding the potential synergistic effect of fosfomycin against a total of 34 *Acinetobacter baumannii* strains [22]. Specific data are shown in Table 3. Another study provided data regarding the synergistic effect of fosfomycin with gentamicin against *Escherichia coli* and *Klebsiella* spp. [47]. Specific data are shown in Table 3. Yet, the number of the evaluated strains was limited—30 and 12 strains, respectively. Data regarding *Salmonella* and *Shigella* strains were also reported in this study [47]. A synergistic effect for the combination of fosfomycin with amikacin was observed in 82.2% of the 90 evaluated *Salmonella* strains. Data regarding the synergistic effect of fosfomycin with carbenicillin and gentamicin against *Serratia marcescens* were provided in two studies [47, 49]. The findings were discordant; specific data are shown in Table 3.

Discussion

The findings of our study imply that the combination of fosfomycin with other antibiotic agents may provide a

Table 2 Data retrieved from the studies examining the synergistic effect between fosfomycin and specific other antimicrobial agents for Gram-positive bacterial strains^a

Antibiotics	n/N (%) [ref]
MRSA	
Ampicillin	7/32 (21.8) [13]
Cefamandole	97/148 (65.5) [42], 10/10 (100) [43], 50/50 (100) [44]
Cefazolin	66/70 (94.2) [31], 11/25 (44) [30]
Cefmetazole	26/32 (81.2) [13], 45/70 (64.2) [31], 10/14 (71.4) [41]
Cefotaxime	9/14 (64.2) [41], 10/10 (100) [43], 1/1 [46]
Cefotiam	7/32 (21.8) [13]
Cefperazone	10/10 (100) [43]
Ceftriaxone	20/30 (66.6) [36]
Ciprofloxacin	14/18 (77.7) [29]
Fusidic acid	0/24 (0) [26]
Gentamicin	10/148 (6.7) [42]
Imipenem	16/32 (50) [13]
Linezolid	4/5 [10]
Methicillin	46/148 (31) [42]
Oxacillin	3/16 (18.7) [19]
Rifampicin	15/19 (78.9) [29], 0/50 (0) [44]
Sparfloxacin	0/16 (0) [19]
Sulbactam/ cefoperazone	19/32 (59.3) [13]
Trimethoprim	4/148 (2.7) [42]
Vancomycin	32/32 (100) [13], 0/148 (0) [42], 10/50 (20) [44]
<i>Staphylococcus aureus</i>	
Ceftriaxone	2/6 [35], 11/23 (47.8) [36], 0/3 [37], 0/2 [40]
Ciprofloxacin	19/37 (51.3) [38]
Imipenem	10/20 (50) [39]
Vancomycin	1/15 (6.6) [32], 0/5 [15]
Gentamicin	0/29 (0) [47]
Rifampicin	13/38 (34.8) [47], 5/5 [15]
Coagulase-negative staphylococci	
Ciprofloxacin	12/19 (63.1) [29]
Imipenem	10/10 (100) [39]
Rifampin	7/15 (46.6) [29]
Vancomycin	1/18 (5.5) [32]
<i>Streptococcus</i> spp.	
Penicillin	17/56 (30.4) [21], 9/51 (17.6) [23]
Cefazolin	3/56 (5.3) [21]
Cefepime	0/56 (0) [21]
Cefminox	33/56 (58.9) [21]
Cefotaxime	3/56 (5.4) [21], 3/7 (42.9) [28]
Cefotiam	20/56 (35.7) [21]
Ceftriaxone	0/26 (0) [25], 0/4 [37]
Imipenem	1/56 (1.8) [21], 0/26 (0) [25]
Vancomycin	0/26 (0) [28]

Table 2 (continued)

Antibiotics	n/N (%) [ref]
<i>Enterococcus</i> spp.	
Cefotaxime	45/50 (90.0) [24]
Daptomycin	20/64 (31.3) [33]
Imipenem	19/36 (52.7) [39]

n/N Number of isolates exhibiting synergism between fosfomycin and the examined antimicrobial agent/total number of isolates examined in the included study

^a In cases where fewer than 10 bacterial strains were evaluated, percentages are not displayed in the table

useful alternative regarding the treatment of patients with Gram-negative or Gram-positive infections, including MRSA infection. However, the evaluated in vitro data, generated mainly from old studies, do not prove directly the in vitro synergism of fosfomycin with other antibiotic agents against the above-mentioned infections. Additionally, the considerable heterogeneity among the included studies regarding the definition of synergy and the methodology used hampers the establishment of firm conclusions, as well as the extrapolation of the in vitro findings into clinical practice.

Fosfomycin is an antibiotic agent that has been mainly used for the treatment of urinary tract infections. Specifically, fosfomycin tromethamine is approved as an oral single-dose treatment for acute uncomplicated cystitis [50]. Moreover, fosfomycin may also be a useful treatment option for specific types of resistant uropathogens that exhibit considerably high rates of resistance due to the production of extended spectrum beta-lactamases (ESBLs) [51, 52]. However, recent studies suggest that mutations occurring among populations of uropathogens and specifically among populations of ESBL producers may result in the emergence of resistance to fosfomycin [53, 54]. Indeed, the issue of emergence of resistance is one of significant importance regarding fosfomycin treatment. Resistance of fosfomycin may be attributed to several chromosomal mutations, which mainly affect its uptake [55]. As a result, the potential of a synergistic effect of fosfomycin with another antibiotic agent is an issue of importance, both at a patient and at a community level.

According to a recently published review, pharmacokinetic and pharmacodynamic aspects of fosfomycin, such as the limited binding with serum proteins, the unchanged excretion in the urine, along with the relatively high concentrations that it achieves in the urine, serum, lung, cerebrospinal fluid, and other sites, favor its use for the treatment of relevant infections [56]. Regarding the potential synergistic effect of fosfomycin with other antibiotic agents, fosfomycin appears to have potentially useful pharmacokinetic/pharmacodynamic aspects that favor its use in combination with other antibiotic agents for the treatment of specific infections. In brief, the ability of

Table 3 Data retrieved from the studies examining the synergistic effect between fosfomycin and specific other antimicrobial agents for Gram-negative bacterial strains^a

Antibiotics	n/N (%) [ref]
Non-fermentative Gram-negative strains	
<i>Pseudomonas aeruginosa</i>	
Amikacin	0/26 (0) [16], 2/2 (100) [17], 3/16 (18.8) [20], 8/12 (66.7) [27]
Aztreonam	23/30 (76.7) [14], 7/12 (58.3) [27]
Cefepime	23/30 (76.7) [14]
Ceftazidime	2/18 (11.1) [12], 21/30 (70.0) [14], 7/26 (26.9) [16], 8/12 (66.7) [18], 0/16 (0) [20], 9/12 (75) [27]
Ciprofloxacin	20/74 (27.0) [9], 10/26 (38.4) [16], 6/16 (37.5) [20], 29/37 (78.4) [38], 18/30 (60) [34]
Gentamicin	1/22 (4.5) [12], 21/30 (70.0) [14], 55/77 (71.4) [47]
Imipenem	11/29 (37.9) [12], 22/30 (73.3) [14], 0/16 (0) [20], 4/12 (33.3) [27]
Levofloxacin	1/1 [11], 20/30 (86.9) [14]
<i>Acinetobacter baumannii</i>	
Amikacin	15/34 (38.2) [22]
Ceftazidime	1/34 (2.9) [22]
Ciprofloxacin	1/34 (2.9) [22]
Imipenem	1/34 (2.9) [22]
Enterobacteriaceae	
<i>Escherichia coli</i>	
Gentamicin	4/30 (13.4) [47]
<i>Klebsiella pneumoniae</i>	
Gentamicin	5/12 (41.7) [47]
<i>Salmonella</i> spp.	
Amikacin	74/90 (82.2) [48]
Cefepime	56/90 (62.2) [48]
<i>Serratia marcescens</i>	
Carbenicillin	21/24 (87.5) [49], 9/32 (28.1) [47]
Gentamicin	22/24 (91.6) [49], 5/39 (12.8) [47]
<i>Shigella</i> spp.	
Amikacin	27/50 (48) [48]
Cefepime	29/50 (58) [48]

n/N Number of isolates exhibiting synergism between fosfomycin and the examined antimicrobial agent/total number of isolates examined in the included study.

^a In cases where fewer than 10 bacterial strains were evaluated, percentages are not displayed in the table

fosfomycin to modify the production of penicillin-binding proteins (PBPs) enables its use for the treatment of MRSA infections as well as infections from penicillin-resistant *S. pneumoniae* [23, 41].

The ability of fosfomycin to penetrate biofilm layers encourages the use of fosfomycin in combination with other antibiotics against microbial strains growing on biofilms. Specifically, relevant studies report a synergistic effect of fosfomycin with quinolone antibiotic agents such as ulifloxacin, levofloxacin [11], and ofloxacin against *P. aeruginosa* biofilm isolates [57]. Notably, fosfomycin is synergistic with N-acetylcysteine against *E. coli* biofilm isolates [58].

Another aspect of fosfomycin that could prove useful, when it is used in combination with other antibiotic agents, is its ability to modify the toxicity of many types of co-

administered drugs [56]. Specifically, fosfomycin is reported to mitigate in vivo the toxicity of aminoglycosides [59], glycopeptides [60], as well as polymyxin B [61]. Finally, it has been reported that the synergistic combination with either amoxicillin or clarithromycin may provide a useful alternative treatment option for patients with *Helicobacter pylori* infections [62].

Our study has limitations that should be taken into consideration before the extrapolation of our findings. Firstly, considerable heterogeneity is observed among the included studies regarding the definition of synergy; specifically only 25 of the 41 studies used the fractional inhibitory concentration index as the definition of synergy of fosfomycin with the respective evaluated antibiotics. Heterogeneity was also observed regarding the laboratory

methods, as well as the fosfomycin break points used. Moreover, the majority (34 of the 41) of the included studies were older studies, published during the period 1977–1999. In this regard, we were unable to reach conclusive results regarding specific antibiotic combinations with fosfomycin for the evaluated microorganisms. Despite these shortcomings, the available data are not to be overlooked as they indicate that further research is justified.

In conclusion, in this era of alarmingly high drug resistance, the synergistic combination of fosfomycin with several other antibiotic agents may be a useful alternative treatment option for Gram-negative and Gram-positive infections. However, additional studies with more stringent definitions, as well as studies that will evaluate the clinical efficacy of synergistic combinations of fosfomycin with other antibiotics will contribute to the already available knowledge regarding the role of fosfomycin in synergistic combinations with other antibiotics.

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